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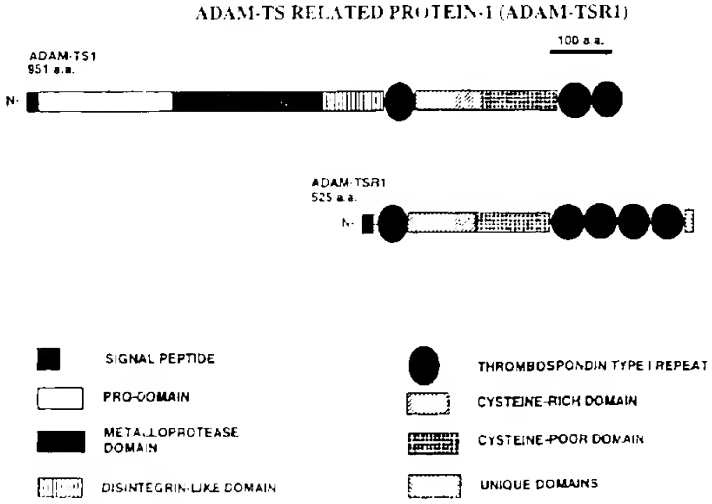
(54) **Title:** NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES



The present invention relates to novel polynucleotides and proteins encoded thereby. More particularly, the present invention relates to nucleic acids which are tissue-specific isoforms of members of the ADAMTS-N proteins. The present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-TS Related protein-1) and the polynucleotides which encode such protein.

NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES

Background of the Invention

This invention relates to isolated nucleic acid molecules which encode proteins belonging to a zinc metalloprotease family. The zinc metalloproteases have been implicated in a variety of diseases and development disorders that involve enhanced or depressed proteolysis of components of the extracellular matrix, receptors, or other extracellular molecules.

More particularly, the invention relates to isolated nucleic acid molecules encoding proteins belonging to a subfamily of zinc metalloproteases referred to as "ADAMTS", an abbreviation for A Disintegrin-like And Metalloprotease domain with ThromboSpondin type I motifs. Proteins in the ADAMTS subfamily all possess a Zn protease catalytic site consensus sequence (HEXXH+H), which suggests an intact catalytic activity for each of these proteins. The ADAMTS proteins also have putative N-terminal signal peptides and lack transmembrane domains, which suggests that the proteins in this subfamily are secreted. The proteins in the ADAMTS subfamily also possess at least one thrombospondin type (TSP1) motif, which suggests a binding of these proteins to components of the extracellular matrix (ECM) or to cell surface components.

Members of the ADAMTS subfamily of proteins are ADAMTS-1, ADAMTS-2, ADAMTS-3, and ADAMTS-4. ADAMTS-1 protein is selectively expressed in colon 26 adenocarcinoma cachexigenic sublines. ADAMTS-1 mRNA is induced by the inflammatory cytokine interleukin-1 in vitro and by intravenous administration of lipopolysaccharide in vivo. Thus, the ADAMTS-1 protein is believed to play a role in tumor

cleavage of native triple-helical procollagen I and procollagen II. The ADAMTS-2 protein also has an affinity for collagen XIV. Lack of the ADAMTS-2 protein is known to cause dermatosparaxis in cattle, or Ehlers-Danlos syndrome type VIIC (EDS-VIIC) in humans. EDS-VIIC is characterized clinically by severe skin fragility, and biochemically by the presence in skin of procollagen which is incompletely processed at the amino terminus. Thus, it is believed that the ADAMTS-2 protein plays a role in processing of procollagen to mature collagen, an essential step for correct assembly of collagen into collagen fibrils. The ADAMTS-3 protein is similar in sequence to ADAMTS-2 and may have similar function.

The ADAMTS-4 protein catalyzes cleavage of the core protein of the extracellular matrix proteoglycan, aggrecan. Aggrecan degradation is an important factor in the erosion of articular cartilage in arthritic disease. Aggrecan fragments have been identified in cultures undergoing cartilage matrix degradation and in arthritic synovial fluids. Therefore, overexpression or activation of ADAMTS-4 protein may be related to both inflammatory and non-inflammatory arthritis.

On the basis of the structure, location, and the demonstrated proteolytic activity of ADAMTS proteins 1-4, it is expected that other members of the ADAMTS subfamily play a role in the cleavage of proteoglycan core proteins that are found in the extracellular matrix, such as, for example, versican, brevican, neuracan, NG-2, aggrecan, as well as molecules such as collagen. It is also expected that other members of the ADAMTS subfamily play a role in embryogenesis, implantation of a fertilized egg, [illegible]

Thus, it is [illegible] of the ADAMTS

subfamily of proteins, the nucleic acids that encode such proteins, and antibodies that are specific for such proteins. Such molecules are useful research tools for studying development of the extracellular matrix during embryogenesis and fetal development, and for studying disorders or diseases that are characterized by improper development of the extracellular matrix or enhanced or reduced destruction of the extracellular matrix. Such molecules, particularly the nucleic acids and the antibodies, are also useful tools for diagnosing such diseases or for monitoring the efficacy of therapeutic agents that have been developed to treat such diseases.

Summary of the Invention

The present invention provides novel, isolated, and substantially purified proteins having the characteristics of an ADAMTS protein. The novel proteins are referred to hereinafter individually as "ADAMTS-5", "ADAMTS-6", "ADAMTS-7", "ADAMTS-8", "ADAMTS-9" and "ADAMTS-10", and collectively as "ADAMTS-N". In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set forth set forth in SEQ ID NO: 2. In another embodiment, ADAMTS-5 is a human ADAMTS-5 protein which comprises amino acid 1 through amino acid 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, mature human ADAMTS-6 protein comprises amino acid 245 through amino acid 860 of SEQ ID NO: 6. In one embodiment, mature human ADAMTS-7 protein comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID NO: 8. In one embodiment, mature ADAMTS-8 protein is a mouse protein which comprises amino acid

forth in SEQ ID NO: 12. In one embodiment, mature ADAMTS-9 protein

is a human protein which comprises amino acid 236 through amino acid 1882 of the sequence set forth in SEQ ID NO: 14. In another embodiment, ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 974 of the sequence set forth in SEQ ID NO: 16. In one embodiment, mature ADAMTS 10 protein is a human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment, ADAMTS-10 protein is a mouse protein which comprises amino acid 1 through amino acid 547 of the sequence set forth in SEQ ID NO: 20

The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-T-S Related protein-1) and the polynucleotides which encode such protein. In one embodiment, the ADAMTS-R1 protein comprises amino acid 1 through amino acid 525 of the sequence set forth in SEQ. ID NO: 22.

Brief Description of the Drawings

Figure 1 shows an amino acid sequence (SEQ ID NO:2) of a full-length mouse ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 1) which encodes such protein.

Figure 2 shows an amino acid sequence (SEQ ID NO:4) of a partial human ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 3) which encodes such protein.

[illegible] encodes such protein.

Figure 4 shows an amino acid sequence (SEQ ID NO:8) of a full-length human ADAMTS-7 protein and a nucleic acid sequence (SEQ ID NO:7) which encodes such protein.

Figure 5 shows an amino acid sequence (SEQ ID NO 10) of a full-length mouse ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO:9) which encodes such protein.

Figure 6 shows an amino acid sequence (SEQ ID NO: 12) of a partial human ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO: 11) which encodes such amino acid sequence

Figure 7 shows an amino acid sequence (SEQ ID NO: 14), of a full-length human ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 13) Which encodes such protein.

Figure 8 shows an amino acid sequence (SEQ ID NO. 16) of a partial mouse ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 15) which encodes such amino acid sequence.

Figure 9 shows an amino acid sequence (SEQ ID NO 18) of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 17) which encodes such protein.

Figure 10 shows an amino acid sequence (SEQ ID NO:20) of a partial mouse ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 19) which encodes such amino acid sequence.

Figure 11 shows an amino acid sequence (SEQ ID NO:22) of a full length ADAMTS-B1 protein and a nucleic acid sequence (SEQ ID NO: 21) which encodes such protein.

Figure 12 depicts the cloning strategy used for isolation of **a.** mouse and human ADAMTS-5 cDNAs **b.** human ADAMTS-6 cDNA and **c.** human ADAMTS-7

[illegible] of alternatively spliced transcripts are shown in the middle

dotted lines. DNA scale marker (in bp) and amino acid scale marker are at upper right. Location of the probe used for in situ hybridization (ISH) is shown in a.

Figure 13 shows the predicted amino acid sequences of **a.** the mouse and human ADAMTS-5 proteins (alignment shows mouse sequence above, partial human sequence below) **b.** ADAMTS-6, and **c.** ADAMTS-7. The active-site sequences and proposed Met-turn are enclosed in boxes. Potential furin cleavage site(s) are indicated by arrows. Thrombospondin type 1 modules are underlined. Potential sites for N-linked glycosylation are overlined. Cysteine residues within the context of an MMP-like "cysteine switch" are indicated by the solid circles. Other cysteine residues are indicated by asterisks. The prodomain extends until the furin cleavage site, and the catalytic domain extends from the furin cleavage site to the approximate start of the disintegrin-like sequence (Dis). The start of the spacer domain is indicated; the region between the N-terminal TS domain and the spacer domain is the cysteine-rich domain. The single letter amino acid code is used.

Figure 14 shows Northern analysis of expression of ADAMTS-5, 6 and 7. RNA kilobase markers are shown at left of each autoradiogram, and tissue origin is indicated above each lane. **a.** Mouse embryo northern blots. b. Human multiple adult tissue northern blots.

Figure 15 is a schematic representation of the domain structure of ADAMTS-R1 protein as compared to ADAMTS-1 protein.

Figure 16 shows an amino acid sequence (SEQ ID NO: 24) of an alternative embodiment of a full length human ADAMTS-16 protein and a

a protein designated as human ADAMTS-R1 and a nucleic acid sequence

(SEQ ID NO: 25) which encodes such protein.

Figure 18 is a schematic representation of the domain structure of human ADAMTS-9b protein as compared to human and mouse ADAMTS-9 protein.

Detailed Description of the Invention

ADAMTS-N Proteins

The present invention relates to novel, isolated, substantially purified, mammalian proteins belonging to the ADAMTS subfamily of metalloproteases. As used herein, the term "substantially purified" refers to a protein that is removed from its natural environment, isolated or separated, and at least 60% free, preferably 75% free, and most preferably 90% free from other components with which it is naturally associated.

The novel mammalian proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively ADAMTS-N. In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set forth in SEQ ID NO: 2. In another embodiment, the ADAMTS-5 protein is a human protein which comprises amino acid 1 through amino acid 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, ADAMTS-6 protein is a mat-Lire human protein which comprises amino acid 245 through amino acid 860 of SEQ ID NO:6. In one embodiment, the ADAMTS-7 protein is a mature human protein which comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID NO: 8. In one embodiment, the ADAMTS-8 protein is a mature mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: 10. In another embodiment, the

forth in SEQ ID NO: 14. In another embodiment, the ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 874 of the sequence set forth in SEQ ID NO: 16. In another embodiment, the ADAMTS-9 designated ADAMTS-9b is a human protein which is comprised of 1934 amino acids as set forth in SEQ ID NO 26. In one embodiment, the ADAMTS-10 protein is a mature human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment the ADAMTS- 10 protein is a mouse protein which comprises amino acid 1 through amino acid 525 of the sequence set forth in SEQ ID NO:20. In another embodiment, the ADAMTS-10 protein is a human protein which is comprised of 1072 amino acids as set forth in SEQ ID NO 24.

All of the novel ADAMTS-N proteins starting at the amino terminus comprise a signal sequence followed by a putative pro region which contains a consensus sequence for furin cleavage (except for ADAMTS-10), a catalytic domain, a domain of 60-90 residues with 35 to 45% similarity to snake venom disintegrins, a TS module, a cysteine rich domain containing multiple conserved cysteine residues, a spacer domain, and one or multiple C terminal TS modules. (See Figure 12.) As determined using the BLAST software from the National Center for Biotechnology Information, the predicted mature forms of the ADAMTS-N proteins show an overall 20-30% similarity to each other and to ADAMTS-1 4, although this may be considerably higher or lower for individual domains as described below.

The ADAMTS-N proteins also encompass variants of the ADAMTS-N proteins shown in Figs. 1-10. A "variant" as used herein, refers to

of the reference sequence. The variant protein has an altered sequence

in which one or more of the amino acids in the reference sequence is deleted or substituted, or one or more amino acids are inserted into the sequence of the reference amino acid sequence. As a result of the alterations, the variant protein has an amino acid sequence which is at least 95% identical to the reference sequence, preferably, at least 97% identical, more preferably at least 98% identical, most preferably at least 99% identical to the reference sequence. Variant sequences which are at least 95% identical have no more than 5 alterations, i.e. any combination of deletions, insertions or substitutions, per 100 amino acids of the reference sequence. Percent identity is determined by comparing the amino acid sequence of the variant with the reference sequence using MEGALIGN project in the DNA STAR program. Sequences are aligned for identity calculations using the method of the software basic local alignment search tool in the BLAST network service (the National Center for Biotechnology Information, Bethesda, MD) which employs the method of Altschul, S. F., Gish, W., Miller, W., Myers, E. W. & Lipman, D. J. (1990) *J. Mol. Biol.* 215, 403-410. Identities are calculated by the Align program (DNAstar, Inc.) In all cases, internal gaps and amino acid insertions in the candidate sequence as aligned are not ignored when making the identity calculation.

While it is possible to have nonconservative amino acid substitutions, it is preferred that the substitutions be conservative amino acid substitutions, in which the substituted amino acid has similar structural or chemical properties with the corresponding amino acid in the reference sequence. By way of example,

e.g. amino acid e.g. serine and threonine with another substitution of

one acidic residue, e.g. glutamic acid or aspartic acid, with another; replacement of one amide-containing residue, e.g. asparagine and glutamine, with another; replacement of one aromatic, residue, e.g. phenylalanine and tyrosine, with another; replacement of one basic residue, e.g. lysine, arginine and histidine, with another; and replacement of one small amino acid, e.g., alanine, serine, threonine, methionine, and glycine, with another.

The alterations are designed not to abolish the immunoreactivity of the variant protein with antibodies that bind to the reference protein. Guidance in determining which amino acid residues may be substituted, inserted or deleted without abolishing immunoreactivity of the variant protein with an antibody specific for the respective reference protein are found using computer programs well known in the art, for example, DNASTAR software.

The ADAMTS-N proteins also encompass fusion proteins comprising an ADAMTS-N protein and a tag, i.e., a second protein or one or more amino acids, preferably from about 2 to 65 amino acids, more preferably from about 34 to about 62 amino acids, which are added to the amino terminus of, the carboxy terminus of, or any point within the amino acid sequence of an ADAMTS-N protein, or a variant of such protein. Typically, such additions are made to stabilize the resulting fusion protein or to simplify purification of an expressed recombinant form of the corresponding ADAMTS-N protein or variant of such protein. Such tags are known in the art. Representative examples of such tags include sequences which encode a series of histidine residues, the epitope tag FLAG, the Herpes simplex

[illegible] amino acids [illegible]

the respective ADAMTS-N protein are altered by posttranslation processes or synthetic methods. Examples of such modifications include, but are not limited to, acetylation, amidation, ADP-ribosylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or a lipid, cross-linking gamma-carboxylation, glycosylation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, sulfation, and transfer-RNA mediated additions of amino acids to proteins such as arginylation and ubiquitination.

The ADAMTS-N proteins are immunogenic and, thus, are useful for preparing antibodies. Such antibodies are useful for identifying and diagnosing disorders which are associated with decreased expression or activity or increased expression of an ADAMTS-N protein. The ADAMTS-N protein may also be useful for treating such disorder.

Diseases involving enhanced or depressed proteolysis of the core proteins of the extracellular may involve enhanced expression or activity or decreased expression or activity of one or more ADAMTS-N proteins. Thus, ADAMTS-N proteins may be used to identify drugs, polypeptides, auto-antibodies, or other natural compounds which bind to an ADAMTS-N protein with sufficient affinity to block or facilitate its activity. The activity of the ADAMTS-N protein is assayed in the presence and the absence of the putative inhibitor or facilitator using any of a variety of protease assays known in the art. In general, the activity of the ADAMTS-N protein is assayed through the use of a peptide or protein substrate having a known or

example, the substrate may be tagged with a fluorescent group on one

side of the cleavage site and with a fluorescence-quenching group on the opposite side of the cleavage site. Upon cleavage by the substrate, quenching is eliminated and a detectable signal is produced. Alternatively, the substrate is tagged with a colorimetric leaving group that more strongly absorbs upon cleavage. Agents which block ADAMTS-N-catalyzed cleavage of a protein substrate may be administered to a subject to block proteolysis of the corresponding protein substrate.

ADAMTS-R1 Protein

The present invention also relates to a protein, referred to hereinafter as "ADAMTS-R1". From its amino to its carboxyl terminus, ADAMTS-R1 comprises a signal peptide sequence, a TS1 module, a cysteine-rich domain, a spacer domain, and three TS1 modules. Thus, ADAMTS-R1 has a structure which is related to or similar to an ADAMTS-N protein, but which lacks a catalytic domain and a disintegrin-like domain. In one embodiment, ADAMTS-R1, protein comprises amino acid 1 through amino acid 525 of the amino acid sequence, SEQ ID NO:22, shown in Fig. 11. Such protein has a 30-40% overall sequence identity with similar regions of the ADAMTS-N proteins. The ADAMTS-R1 proteins also encompass variants of the amino acid sequence shown in Fig. 11 and fusion proteins which contain the amino acid sequence shown in Fig. 11 or a variant thereof. On the basis of its domain organization, it is expected that ADAMTS-R1 can bind to extracellular matrix or cell surface molecules, including ADAMTS-N substrates. Thus, it is expected that ADAMTS-R1 can be used as an cell-matrix or cell-cell adhesion molecule or an ADAMTS-N competitive inhibitor. The ADAMTS-R1

expression or increased expression of an ADAMTS-R1 protein.

Polynucleotides

The present invention also provides isolated polynucleotides which encode the mammalian ADAMTS-N proteins and the mammalian ADAMTS-R1 protein. Figure 1 shows one embodiment of a polynucleotide, SEQ ID NO: 1, which encodes the full-length mouse ADAMTS-5 protein. Figure 2 shows one embodiment of a polynucleotide; SEQ ID NO: 3, which encodes a partial human ADAMTS-5 protein. Figure 3 shows one embodiment of a polynucleotide; SEQ ID NO: 5, which encodes a full-length human ADAMTS-6 protein. Figure 4 shows one embodiment of a polynucleotide; SEQ ID NO: 7, which encodes a full-length human ADAMTS-7 protein. Figure 5 shows one embodiment of a polynucleotide; SEQ ID NO: 9, which encodes a full-length mouse ADAMTS-8 protein. Figure 6 shows one embodiment of a polynucleotide; SEQ ID NO: 11, which encodes a partial human ADAMTS-8 protein. Figure 7 shows one embodiment of a polynucleotide; SEQ ID NO: 13, which encodes a full-length human ADAMTS-9 protein. Figure 8 shows one embodiment of a polynucleotide; SEQ ID NO: 15, which encodes a partial ADAMTS-9 protein. Figure 9 shows one embodiment of a polynucleotide; SEQ ID NO: 17, which encodes a full-length human ADAMTS-10 protein. Figure 10 shows one embodiment of a polynucleotide; SEQ ID NO: 19, which encodes a partial mouse ADAMTS-10 protein. Figure 11 shows one embodiment of a polynucleotide; SEQ ID NO: 21, which encodes a full-length ADAMTS-R1 protein.

Due to the known degeneracy of the genetic code wherein more than one codon can encode the same amino acid, a DNA sequence may vary from that shown in SEQ ID NO: 1 and still encode an ADAMTS-5

in SEQ ID NO:6. Similarly a DNA sequence may vary from that shown in SEQ ID NOS: 7, 9, 11, and 13, and still encode the amino acid sequences shown in SEQ ID NOS: 8, 10, 12, and 14, respectively. Such variant DNA sequence may result from silent mutations, such as for example those that occur during PCR amplification or from deliberate mutagenesis of a native sequence.

The present polynucleotides also encompass polynucleotides having sequences that are capable of hybridizing to the nucleotide sequences of FIGS 1 - 11 under stringent conditions, preferably highly stringent conditions. Hybridization conditions are based on the melting temperature™ of the nucleic acid binding complex or probe, as described in Berger and Kimmel (1987) Guide to Molecular Cloning Techniques, Methods in Enzymology, vol 152, Academic Press. The term "stringent conditions, as used herein, is the "stringency" which occurs within a range from about Tm-5 (5° below the melting temperature of the probe) to about 20° C below Tm. As used herein "highly stringent" conditions employ at least 0.2 x SSC buffer and at least 65° C. As recognized in the art, stringency conditions can be attained by varying a number of factors such as the length and nature, i.e., DNA or RNA, of the probe; the length and nature of the target sequence, the concentration of the salts and other components, such as formamide, dextran sulfate, and polyethylene glycol, of the hybridization solution. All of these factors may be varied to generate conditions of stringency which are equivalent to the conditions listed above.

The present polynucleotides also encompasses alleles of the

[illegible] may include one or more mutations in the [illegible]

ADAMTS-R1 encoding sequence. Such mutations typically arise from natural addition, deletion of substitution of nucleotides in the open reading frame sequences. Any gene which encodes an ADAMTS-N protein or ADAMTS-RI protein may have none, one, or several allelic forms. Such alleles are identified using conventional techniques, such as for example screening libraries with probes having sequences identical to or complementary with one or more ADAMTS-N polynucleotides.

The present polynucleotides also encompass altered polynucleotides which encode ADAMTS-N proteins, ADAMTS-R1 proteins, and variants thereof. Such alterations include deletions, additions, or substitutions. Such alterations may produce a silent change and result in an ADAMTS-N protein having the same amino acid sequence as the ADAMTS-N protein encoded by the unaltered polynucleotide. Such alterations may produce a nucleotide sequence possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eucaryotic host may be incorporated into the nucleotide sequences showing Figures 1 -11 to increase the rate of expression of the proteins encoded by such sequences. Such alterations may also introduce new restriction sites into the sequence or result in the production of an ADAMTS-N or ADAMTS-PI variant. Typically, such alterations are accomplished using site-directed mutagenesis.

The polynucleotides are useful for producing ADAMTS-N or ADAMTS-R1 proteins. For example, an RNA molecule encoding an ADAMTS-N protein is used in a cell-free translation systems to prepare such

[illegible] recombinant and synthetic DNA [illegible]

SV40, bacterial plasmids, phage DNAs; yeast plasmids, vectors derived from combinations of plasmids and phage DNAs, viral DNA such as vaccinia, adenovirus, fowl pox virus, pseudorabies, baculovirus, and retrovirus. The DNA sequence is introduced into the expression vector by 5 conventional procedures.

Accordingly, the present invention also relates to recombinant constructs comprising one or more of the present polynucleotide sequences. Suitable constructs include, for example, vectors, such as a plasmid, phagemid, or viral vector, into which a sequence that encodes an ADAMTS-N protein or an ADAMTS-R1 protein has been inserted. In the expression vector, the DNA sequence which encodes the ADAMTS-N protein is operatively linked to an expression control sequence, i.e., a promoter, which directs mRNA synthesis. Representative examples of such promoters, include the LTR or SV40 promoter, the *E. coli* lac or trp, the phage lambda PL promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or in viruses. The promoter may also be the natural promoter of the ADAMTS-N encoding sequence. The expression vector, preferably, also contains a ribosome binding site for translation initiation and a transcription terminator. Preferably, the recombinant expression vectors also include an origin of replication and a selectable marker, such as for example, the ampicillin resistance gene of *E. coli* to permit selection of transformed cells, i.e. cells that are expressing the heterologous DNA sequences. The polynucleotide sequence encoding the ADAMTS-N protein is incorporated into the vector in frame with translation

[illegible] art. Such techniques are described in Sambrook, J. et al.

(1989) Molecular Cloning A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y. and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wile & Sons, New York, NY.

Polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein may also be used for diagnostic purposes. The polynucleotides may be used to detect and quantify ADAMTS-N or ADAMTS-R1 gene transcripts in biopsied tissues in which enhanced expression or reduced expression of the corresponding ADAMTS-N or ADAMTS-RI gene is correlated with a disease. The diagnostic assay may be used to determine whether expression is absent, present, or altered and to determine whether certain therapeutic agents modulate expression of the corresponding ADAMTS-N or ADAMTS-R1 gene.

Also encompassed by the present invention, are single stranded polynucleotides, hereinafter referred to as antisense polynucleotides, having sequences which are complementary to the DNA and RNA sequences which encode the ADAMTS-N or ADAMTS-R1 proteins. The term complementary as used herein refers to the natural binding of the polynucleotides under permissive salt and 5 temperature conditions by base pairing.

The present invention also encompasses oligonucleotides that are used as primers in polymerase chain reaction (PCR) technologies to amplify transcripts of the genes which encode the ADAMTS-N and ADAMTSR-1 proteins or portions of such transcripts. Preferably, the primers comprise 18-30 nucleotides, more preferably 19-25 nucleotides. Preferably, the primers have a G+C content of 40% or greater. Such oligonucleotides are at least 98% complementary with a

sense strand or its corresponding antisense strand. Primers which are which have 100% complementarity with the antisense strand of a double-stranded DNA molecule which encodes an ADAMTS-N protein have a sequence which is identical to a sequence contained within the sense strand. The identity of primers which are 15 nucleotides in length and have full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences, shown in FIG I - 11 and described by the general formula a-b; where a is any integer between I and the position number of the nucleotide which is located 15 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -11; where b is equal to a+14; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIGS 1 - 11.

The present invention also encompasses oligonucleotides that are useful as hybridization probes for for isolating and identifying cDNA clones and genomic clones encoding the ADAMTS-N or ADAMTS-R1 protein or allelic forms thereof. Such hybridization probes are also useful for detecting transcripts of the genes which encode the ADAMTS-N family proteins or for mapping of the genes which encode the ADAMTS-N proteins Preferably, such oligonucleotides comprise at least 210 nucleotides, more preferably at least 230, most preferably from about 210 to 280 nucleotides. Such hybridization probes have a sequence which is at least 90% complementary with a sequence contained within the sense strand of a DNA molecule which encodes an ADAMTS-N protein or ADAMTS-R1 protein or with a sequence contained

Tm of the probe) to about 20°C to 25°C below Tm. The probes are used in Northern assays to detect transcripts of ADAMTS-N homologous genes and in Southern assays to detect ADAMTS-N homologous genes. The identity of probes which are 200 nucleotides 5 in length and have full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences shown in FIG 1 - 10 and described by the general formula a-b; where a is any integer between 1 and the position number of the nucleotide which is located 200 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -10; b is equal to a +200; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIG 1-10.

Such probes or primers are also useful for identifying tissues or cells in which the corresponding ADAMTS-N or ADAMTS-R1 gene is preferentially expressed either constitutively or at particular state of tissue differentiation or development or in disease states. Expression of the ADAMTS-N or ADAMTS-R1 gene in a particular tissue or group of cells is determined using conventional procedures including, but not limited to, Northern analysis, in situ hybridization to RNA or RT-PCR amplification. Isolated polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein are also useful as chromosome markers to map linked gene positions to identify chromosomal aberrations such as translocations, inversions and trisomies, to compare with endogenous DNA sequences in patients to identify potential genetic disorders, and as probes to hybridize

and chromosomes, PCR, and allele specific hybridization.

Antibodies

In another aspect, the present invention relates to antibodies which are specific for and bind to the ADAMTS-5 protein, the ADAMTS-6 protein, the ADAMTS-7 protein, the ADAMTS-8 protein, the ADAMTS-9 protein, the ADAMTS-10 protein, or the ADAMTS-R1 protein. Such antibodies are useful research tools for identifying *tissues that contain elevated levels of the respective protein and for purifying the respective protein from cell or tissue extracts, medium of cultured cells, or partially purified preparations of intracellular and extracellular proteins by affinity chromatography. Such antibodies are also useful for identifying and diagnosing diseases associated with elevated or reduced levels of an ADAMTS-N protein or ADAMTS-R1 protein. Such antibodies are also useful for monitoring the effect of therapeutic agents on the synthesis and secretion of ADAMTS-N proteins by cells in vitro and in vivo. Such antibodies may also be employed in procedures, such as co-immunoprecipitation and co-affinity chromatography, for identifying other proteins, activators and inhibitors which bind to an ADAMTS-N or ADAMTS-R1 protein.

The present invention also provides a method for detecting an ADAMTS-N or ADAMTS-R1 protein, in a bodily sample from a patient using antibodies immunospecific for an ADAMTS-N or ADAMTS-R1 protein. The method comprises contacting the antibody with a sample taken from the patient; and assaying for the formation of a complex between the antibody and the corresponding ADAMTS-N or ADAMTS-R1 protein present in the sample. The sample may be a tissue or a biological fluid,

tissue, cells obtained from swabs and smears. To monitor changes in expression of the ADAMTS-N protein during fetal development and pregnancy, it is preferred that the sample be amniotic fluid. To monitor changes in expression of the ADAMTS-N protein during joint disorders, the preferred sample is synovial fluid. To monitor changes in expression of ADAMTS-N proteins during cancer, the preferred samples include, but are not limited to, serum, body fluids, or biopsy tissue. To monitor changes in expression of ADAMTS-N proteins during inflammation the preferred samples include, but are not limited to, serum, body fluids, or biopsy tissue.

The sample may be untreated, or subjected to precipitation; fractionation, separation, or purification before combining with the anti-ADAMTS-N protein antibody. For ease of detection, it is preferred that isolated proteins from the sample be attached to a substrate such as. a column, plastic dish, matrix, or membrane, preferably nitrocellulose. Preferably, the detection method employs an enzyme-linked immunosorbent assay (ELISA) or a Western immunoblot procedure.

Interactions between an ADAMTS-N protein in the sample and the corresponding anti ADAMTS-N antibody are detected by radiometric, colorimetric or fluorometric means, size separation, or precipitation. Preferably, detection of the antibody-ADAMTS-N protein complex is by addition of a secondary antibody that is coupled to a detectable tag, such as for example, an enzyme, fluorophore, or chromophore. Formation of the complex is indicative of the presence of the ADAMTS-N protein i n the test sample. Thus,

[illegible] quantify the amount of the ADAMTS-N protein in the test sample.

Deviation between control and test values establishes the parameters for diagnosing the disease.

Preparing the ADAMTS-N proteins and the ADAMTS-R1 protein

The ADAMTS-N proteins and the ADAMT-SR1 protein may be produced by conventional peptide synthesizers. The ADAMTS-N proteins and the ADAMTS-R1 protein may also be produced using cell-free translationsystems and RNA molecules derived from DNA constructs that encode an ADAMTS-N protein or an ADAMTS-RI protein. Alternatively, ADAMTS-N proteins are made by transfecting host cells with expression vectors that comprise a DNA sequence that encodes the respective ADAMTS-N protein and then inducing expression of the protein in the host. cells. For recombinant production, recombinant constructs comprising one or more of the sequences which encode the ADAMTS-N protein or a variant thereof are introduced into host cells by conventional methods such as calcium phosphate transfection, DEAE-dextran mediated transfection, transvection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape lading, ballistic introduction or infection.

The ADAMTS-N protein and the ADAMTS-R1 protein may be expressed in suitable host cells, such as for example, mammalian cells, yeast, bacteria, insect cells or other cells under the control of appropriate promoters using conventional techniques. Suitable hosts include, but are not limited to, E. coli, P. pastoris, Cos cells and 293 HEK cells. Following transformation of the suitable host strain and growth of the host strain to an appropriate cell density, the cells are harvested by centrifugation, disrupted by physical or

cell pellets or from cell culture medium, followed by salting-out, and one or more chromatography steps, including aqueous ion exchange chromatography, size exclusion chromatography steps, and high performance liquid chromatography (HPLC), and affinity chromatography may be used to isolate the recombinant ADAMTS-N protein or ADAMTS R1 protein

Preparation of Antibodies

The ADAMTS-N proteins, and variants thereof are used as immunogens to produce antibodies immunospecific for one or more ADAMTS-N protein. The term "immunospecific" means the antibodies have substantially greater affinity for one or more ADAMTS-N protein than for other proteins. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, and Fab fragments.

Antibodies are also prepared using an oligopeptide having a sequence which is identical to a portion of the amino acid sequence of an ADAMTS-N protein. Preferably the oligopeptide has an amino acid sequence of at least five amino acids, and more preferably, at least 10 amino acids that are identical to a portion of the amino acid sequence of an ADAMTS-N protein. Such peptides are conventionally fused with those of another protein such as keyhole limpet hemocyanin and antibody produced against the chimeric molecule. One preferred oligopeptide for preparing an antibody to mouse ADAMTS-5 has the sequence (C)HIRVRQFKAVIQTRF, SEQ ID NO: 30. Another preferred oligopeptide for preparing an antibody to ADAMTS-5 is CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO: 3 1. One preferred oligopeptide for preparing an antibody to ADAMTS-6 has the sequence

preparing an antibody to ADAMTS-8 has the sequence CVKEDVENPKAVVDGDWGP, SEQ ID NO:25. One preferred oligopeptide for preparing an antibody to ADAMTS-9 has the sequence QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26. Another preferred oligopeptide for preparing an antibody to ADAMTS-9 has the sequence PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27. One preferred oligopeptide for preparing an antibody for ADAMTS-R1 has the sequence QELEEGAAVSEEPS, SEQ ID NO:28. Another preferred oligopeptide for preparing an antibody for ADAMTS-R1 has the sequence YYPENIKPKPKLQE; SEQ ID NO:29.

Polyclonal antibodies are generated using conventional techniques by administering the ADAMTS-N protein or achimeric molecule to a host animal. Depending on the host species, various adjuvants may be used to increase immunological response. Among adjuvants used in humans, Bacilli Calmette-Guerin (BCG), and Corynebacterium parvum. are especially preferable. Conventional protocols are also used to collect blood from the immunized animals and to isolate the serum and or the IgG fraction from the blood.

For preparation of monoclonal antibodies, conventional hybridoma techniques are used. Such antibodies are produced by continuous cell lines in culture. Suitable techniques for preparing monoclonal antibodies include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV hybridoma technique.

Various immunoassays may be used for screening to identify antibodies having the desired specificity. These include protocols which involve competitive binding or immunoradiometric assays and

Polynucleotides encoding specific membrane binding ADAMTS-N

protein or an ADAMTS-Rl protein may be synthesized in whole or in part using chemical methods. Polynucleotides which encode an ADAMTS-N protein, particularly alleles of the genes which encode the ADAMTS-N protein, may be obtained by screening a genomic library or cDNA library with a probe comprising sequences identical or complementary to the sequences shown in Figures 1 - 10 or with antibodies immunospecific for a ADAMTS-N protein to identify clones containing such polynucleotide.

Example 1 ADAMTS-512 protein

A cDNA encoding mouse ADAMTS-5 protein was obtained using IMAGE Clone 569515, purchased from Research Genetics, Huntsville, Alabama and 7 day old mouse embryo cDNA library from Clontech, Palo Alto, CA. A cDNA encoding human ADAMTS-5 protein was obtained using IMAGE Clone 345484 purchased from Research Genetics, Huntsville, Alabama and a human fetal brain cDNA from Clontech. The clone inserts were sequenced in their entirety. Using oligonucleotide primers based on the sequences at the ends of the clone inserts as template, successive rounds of RACE (Rapid Amplification of cDNA Ends) by PCR was performed at 5' and 3 ends. RACE primers were generated 50-200 bp from the ends of the sequences so that the contiguity of RACE clones with the I.M.A.G.E. clone could be clearly established. A single round of 5' and 3' 20 RACE sufficed for cloning of the entire coding sequence of the mouse ADAMTS-5 protein and part of the catalytic zinc binding site through to the stop codon of the human ADAMTS-5 protein. Primers were designed with calculated Tm>72°C and RACE was performed with nested primers for each amplification. PCR used the Advantage PCR reagents (Clontech, Palo Alto, CA); the

[illegible] RACE [illegible]

conditions; 95°C for 1 minute followed by 5 cycles of 95°C for 0.5 minutes, 72°C for 5 minutes, then 5 cycles of 95°C for 0.5 minutes, 70°C for 5 minutes and 20 cycles of 95°C for 0.5 minutes, 68°C for 5 minutes. The PCR products were analyzed by Southern blotting, initially using [α^{32}P]-dCTP labeled.

Hybridizing bands were ligated into pGEM-T Easy (Promega, Madison, WI) and individual clones were selected by another round of Southern analysis. Automated nucleotide sequencing of both strands of each clone were done at the Molecular Biotechnology Core of the Lerner Research Institute, Cleveland Clinic Foundation and nucleotide sequence data were analyzed using the DNAStar software. By integration of the overlapping sequences thus obtained, a contiguous nucleotide sequence was determined. The nucleotide sequence of the mouse ADAMTS-5 cDNA and the predicted amino acid sequence of the protein encoded by this cDNA are shown in Fig. 1. The nucleotide sequence of the human ADAMTS-5 cDNA and the predicted partial amino acid sequence of the protein encoded by this cDNA are shown in Fig. 2.

The predicted molecular mass (Mr) of the mature ADAMTS-5 protein is 73717.50 daltons. It is expected that the actual Mr of the active ADAMTS-5 protein is different due to post-translational modification, which could potentially increase the Mr. The predicted domain organization of ADAMTS-5 protein relative to the cloned cDNA is shown in Figure 12. The pro-domain of the full-length mouse ADAMTS-5 protein has 3 consensus cleavage signals for furin. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the

1. Five cysteine residues are upstream of the zinc binding sequence

while three residues are downstream, an arrangement that is shared with other ADAMTS members. The zinc binding signature is followed by a "Met-turn". The catalytic domain is followed by a domain with 35% similarity to snake venom disintegrins. The disintegrin domain contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain, designated "CRD", to distinguish it from the cysteine-free spacer domain. The CRD contains ten conserved cysteines and demonstrates high sequence homology with the CRD of other ADAMTS-N proteins. The spacer domain of mouse ADAMTS-5 is 158 amino acids in length and is followed by a second TS module. ADAMTS-5 contains three potential glycosylation sites in the mature protease one of which is just upstream of the start of the spacer domain and the second lies within the spacer domain and the third is near the start of the disintegrin domain. The human ADAMTS-5 protein and the mouse ADAMTS-5 protein have 96% sequence identity. ADAMTS-5 bears 46% sequence identity to ADAMTS-4 (KIAA0688), which is characterized as being involved in catabolism of aggrecan core protein in arthritis and 60% identity to ADAMTS-1 which is involved in inflammation.

Example 2 ADAMTS-6

The nucleotide sequence of a human cDNA encoding the full-length ADAMTS-6 protein was obtained using IMAGE clone 742630, which encodes EST AA400393, and a human fetal brain cDNA from Clontech. RACE was performed as described above in Example 1. The I.M.A.G.E. clone 742630 contained an ORF flanked by consensus splice sequences, indicating the presence of introns. Two successive rounds of RACE at the 5' end and a single round of RACE at the 3' end provided the

The nucleotide sequence of the ADAMTS-6 DNA is shown in Fig. 3 The predicted amino acid sequence, SEQ ID NO:6, of the ADAMTS-6 protein is also shown in Fig. 3. The predicted Mr of the full-length, unprocessed ADAMTS-6 protein is 97,115 daltons., and the predicted Mr of the mature ADAMTS-6 protein is 68412.10 daltons. The domain organization of the ADAMTS-6 protein is shown in Fig. 12. The pro-domain of the full-length ADAMTS-6 protein has one consensus cleavage signal for furin. The catalytic domain of the ADAMTS-6 contains six cysteine residues and the reprolysin -zinc binding signature sequence, HEIVHNFGMNHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 35% similarity to snake venom disintegrins. The disintegrin domain contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserve CRD sequence which contains ten conserved cysteines and demonstrates high sequence homology with the CRD of other ADAMTS proteins. The spacer domain of ADAMTS-6 is 127 amino acids in length and is followed by a second TS module. ADAMTS-6 contains four potential glycosylation sites within the pyo-domain and two in the mature protease one of which is in the cysteine rich domain and the other of which is in the spacer domain. ADAMTS-6 bears 46% sequence identity to ADAMTS-1, which is involved in inflammation.

Example 3 ADAMTS-7.

The nucleotide sequence of a cDNA encoding an ADAMTS-7 protein was obtained using IMAGE clone 272098, which encodes EST N4.8032, and a human fetal brain cDNA from Clontech. RACE was performed as described above in Example 1. The I.M.A.G.E. clone 272098 encoded a

methionine codon lies within a satisfactory Kozak consensus for translation initiation.

The nucleotide sequence of the ADAMTS-7 cDNA is shown in Fig. 4. The predicted amino acid sequence, SEQ ID NO: 8, of the ADAMTS-7 protein is also shown in Fig. 4. The predicted Mr of the hill-length, unprocessed ADAMTS-7 protein is 116,607 daltons, and the predicted Mr of the mature ADAMTS-7 protein is 84005 daltons. The domain organization of the ADAMTS-7 protein is shown in Fig. 12. The pro-domain of the full length ADAMTS 7 protein has one consensus cleavage signal for furin. The catalytic domain of the ADAMTS-7 protein contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HELGHSFGIQHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins The disintegrin domain contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserved CRD sequence which contains ten conserved cysteines. The spacer domain of ADAMTS-7 is 221 amino acids in length and is followed by a second TS module and a short sequence containing two cysteine residues. ADAMTS-7 contains three potential glycosylation sites within the mature protease; one of which is just upstream of the spacer domain and one of which is within the spacer domain. ADAMTS-7 bears 35 % sequence identity to ADAMTS-1, which is characterized as being involved in inflammation and 32% identity to ADAMTS-2 which is a procollagen processing enzyme.

Example 4: ADAMTS-8

A nucleotide sequence of a cDNA encoding a partial ADAMTS-8 human

protein was obtained using IMAGE clone 2119838, which encodes EST AI400905, and a human fetal brain cDNA library from Clontech. RACE was performed, as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-8 mouse protein and the amino acid sequence of such protein is shown in Fig. 5. The nucleotide sequence of the cDNA encoding the partial ADAMTS-8 human protein and the amino acid sequence of such protein is shown in Fig. 6.

The predicted Mr of the full-length, unprocessed ADAMTS-8 mouse protein is 1260693 daltons, and the predicted Mr of the mature ADAMTS-8 protein is 68412.10 daltons. The pro domain of the full-length ADAMTS-8 protein has one consensus cleavage signal for furin. The catalytic domain contains eight cysteine residues and the reprolysm-zinc binding signature sequence, HELGHVLSMPHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 20-30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-8 is 146 amino acids in length and is followed by a second TS module. The ADAMTS-8 protein contains 4 potential glycosylation sites within the mature protease: one is in the cysteine-rich domain; one is in the catalytic domain; and two are in the disintegrin-like domain. ADAMTS-8 bears 46% sequence identity to ADAMTS-1 and 42% identity to ADAMTS-4.

Example 5: ADAMTS-9

The nucleotide sequence of a cDNA encoding a full-length, human

[illegible]

protein was obtained using IMAGE clone 535663, which encodes EST AA1 06215, and a mouse cDNA library obtained from Clonetech. RACE was performed as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-9 human proteinand the amino acid sequence of such protein is shown in Fig.6. The nucleotide sequence of the cDNA encoding the partial ADAMTS-9 mouse protein and the amino acid sequence of such protein is shown in Fig. 7.

The predicted Mr of the mature human ADAMTS-9 protein is 169777.20 daltons. The prodomain of the predicted ADAMTS-9 protein has 3 consensus cleavage signal for furin. The catalytic domain of the ADAMTS-9 contains eight cysteine residues and the reprolysin - zinc binding signature sequence, HELGHVFNMPHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 25-30% similarity to snake venom disintegrins The disintegrin domain contains eight cysteine residues. The first TS repeat contains is followed by a conserved CRD sequence which. contains 10 conserved cysteines. The spacer domain of ADAMTS-9 is 124 amino acids in length and is followed by 14 additional TS modules and a C-terminal domain. The ADAMTS-9 protein contains 6 potential glycosylation sites within the mature protease: one in the spacer domain, one in TSP 1 -7, one in TSPI-8, and 3 in the C-terminal domain. The ADAMTS-9 bears 44% sequence identity to ADAMTS-4.

Example 6: ADAMTS-10

The nucleotide sequence of a cDNA encoding a full-length ADAMTS- 10 protein was obtained using IMAGE clone 110403, which encodes EST AA588434, and a human fetal brain cDNA from Clonetech. The nucleotide sequence of a cDNA encoding a partial, mouse ADAMTS-10 protein was obtained using IMAGE clone 1077653, which encodes EST

performed as described above in Example 1. The nucleotide sequence of the human ADAMTS-10 cDNA and the predicted amino acid sequence, SEQ ID 18, of the human ADAMTS-10 protein encoded by such DNA is shown in Fig. 9. The nucleotide sequence of the cDNA encoding the partial mouse ADAMTS-10 protein and the amino acid sequence of such protein is shown in Fig. 10.

The predicted Mr of the mature ADAMTS-10 protein is 95238 daltons. The pro-domain of the full-length ADAMTS-10 protein has no consensus cleavage signal for furin. The catalytic domain of the ADAMTS-10 contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HEIGHTFGMNHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by a conserved CRD sequence which contains 8 conserved cysteines. The spacer domain of ADAMTS-10 is followed by 4 additional TS modules and a Kunitz domain. The ADAMTS-10 protein contains 2 potential glycosylation sites within the mature protease: one in the catalytic domain, and one in the TS 1-3 domain. ADAMTS-10 bears approximately 40% sequence identity to ADAM-TS1, which is characterized as being involved in inflammation.

Comparison of the ADAMTS-N Proteins.

As shown in Figure 11, the ADAMTS-5, ADAMTS-6, and ADAMTS-7 proteins share a common domain organization. From amino to carboxyl termini, they are as follows:

1. **A pre-pro region.** A typical signal sequence of variable length is followed by a putative pro-region of variable length but

context similar to the cysteine "switch" of the MMPs. All three novel cDNAs predict consensus cleavage signals for furin, three in the case of ADAMTS-5, and one each in the case of ADAMTS-6 and ADAMTS-7. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protease. The amino terminus of the mature proteins is predicted to start at the residue immediately following the cleavage sites.

2. **A catalytic domain.** The catalytic domains are very similar to each other and contain eight cysteine residues and a typical reprolysin-type zinc binding signature followed by a "Met-turn". Five cysteine residues are upstream of the zinc binding sequence, while three residues are downstream, an arrangement that is shared with other ADAMTS members. The methionine of the met-turn is not at a constant distance from the zinc-binding signature, but in all three novel proteases, a constant cysteine residue is present in that interval.

3. **A disintegrin-like domain.** The catalytic domain is followed by a domain of 60-90 residues with 35-45% similarity to snake venom disintegrins, but without the canonical cysteine arrangement seen in the latter. This disintegrin-like domain is of comparable length in ADAMTS-5 and ADAMTS-7, it is considerably shorter in ADAMTS-6.

4. **A TS module.** The first TS repeat is very similar in all three novel proteases and very similar to the first TS repeat of other ADAMTSs. It contains the same number of residues (fifty-two) in all three novel proteins.

5. **The cysteine-rich domain.** This TS domain is followed by a

other domains. It shows the least homology of all the domains.

7. **A C-terminal TS module.** The sequence of the second TS module is more variant between the members of the ADAMTS family than the first TS module, despite the conservation of the number and spacing of cysteine residues.

Overall, the predicted mature forms of these proteases show 20-30% similarity to each other and to ADAMTS1-4 although this may be considerably higher or lower for individual domains as described above.

ADAM-TS9 and ADAM-TS10 contain all the domains present in ADAMTS-5 through ADAMTS-8. In addition, ADAMTS-9 and ADAMTS-10 contain the following domains:

A. ADAMTS-9: After the c-terminal TS1 domain which is present in ADAMTS5-8, ADAMTS-9 contains 13 additional and homologous TS11 domains, thus, ADAMTS-9 contains a total of 15 TS1 domains, of which 14 are adjacent to each other in the c-terminal half of the molecule. The 15th TS1 domain from the N-terminus is followed by a unique c-terminal domain which does not possess recognizable domain structure and contains 196 residues including 9 cysteine residues.

B. ADAMTS-10: After the c-terminal TS1 domain which is present in ADAMTS 8, ADAMTS-10 contains 3 additional and homologous TS1 domains, thus, that ADAMTS-10 contains a total of 5 TS1 domains, of which 4 are adjacent to each other in the c-terminal half of the molecule. The 5th TS 1 domain from the N-terminus is followed by an additional 47 amino acid residues including six (6) cysteine residues. These 47 residues have sequence similarity of 30%-40% to

from human and mouse tissues (Clontech, Palo Alto, CA) were hybridized to the [α^{32}P]-dCTP labeled inserts of I.M.A.G.E. clones as per the manufacturer's recommendations followed by autoradiographic exposure for 3-7 days.

In situ hybridization used cryosections of mouse embryos of gestational age 8.5 days and 10.5 days. Embryos were collected with the inclusion of the surrounding uterus and fixed overnight in 4% paraformaldehyde. Sense and anti-sense probes continuously labeled with digoxigenin-UTP (Boehringer-Mannheim, Indianapolis, IN) were transcribed with T7 and T3 RNA polymerases, respectively, using as template a 630 bp EcoRI-SacI fragment from the *Adamts-5* clone 569515 (Fig. 14) cloned into pBluescript SK+ (Stratagene, La Jolla, CA). In situ hybridization was done essentially as previously described in Apte, et al. (1997) J. Biol. Chem. 272:2551-25517, which is specifically incorporated herein by reference, except that sections were predigested with proteinase K (Boehringer-Mannheim, Indianapolis, IN) at a lower concentration (1-5 µg/ml) than reported in Apte, et al.. Bound, digoxigenin-labeled probe was detected using an alkaline phosphatase tagged anti-digoxigenin antibody (Boehringer-Mannheim, Indianapolis, IN) and nuclei were counterstained with methyl green.

Specific hybridization of the antisense Adamts 5 probe to sections of 8.5 day-old mouse embryos was obtained, whereas only low background staining was noted with the control sense probe. Staining was uniform throughout the 8.5 day old embryos. In addition, there was labeling of mRNA in trophoblastic cells lining the uterine cavity

embryos. Labeling was widespread but less intense compared to the

day-old embryo. Labeled cells were seen in mesenchyme and somites as well as in the neural tube and developing hindgut. Northern analysis also indicated that mRNA encoding ADAMTS-5 was present in human placenta but was barely detectable in adult lung, heart, brain, liver, skeletal muscle, kidney and pancreas.

Northern analysis showed undetectable expression of *Adamts-6* during mouse embryo development. Northern analysis indicated that mRNA encoding ADAMTS-6 was present in human placenta but was barely detectable in adult lung, heart, brain, liver, skeletal muscle, kidney and pancreas. *Adamts-7* was expressed at low levels throughout mouse development. In adult human tissues examined with human cDNA probes, ADAMTS-7 mRNA was found in all tissues examined, i.e. in lung, heart, brain, liver, skeletal muscle, kidney, pancreas and placenta. The sizes of the mRNA species recognized by the probes varied. ADAMTS-5 mRNA was approximately 10 kbp in size in human tissue. The most prominent *Adamts-5* species was estimated at 7.5 kbp together with additional bands at 10 kbp and 4.5 kbp. The lone mRNA species detected by ADAMTS-6 probe was approximately 8.5 kbp, whereas the most common mRNA species detected by ADAMTS-7 probe 5 was 5 kbp in size with an additional species seen at 7 kbp in skeletal muscle.

In mouse, ADAMTS-8 is expressed during fetal development (days 7, 11, 15, 17) and in adult mouse lung and heart with an mRNA size of approximately 3.8 kbp. In adult human tissue, ADAMTS-8 is expressed in lung and brain but not in heart, muscle, kidney, colon or thymus. The mRNA size is 3.8 kbp.

ADAMTS-9 is expressed in lung, ovary placenta, heart, brain,

1 alternatively spliced short form of ADAMTS-

ADAMTS-10 is expressed in thymus, prostate, testis, ovary, small intestine, colon, peripheral blood leukocytes, heart, brain, placenta, lung, liver, muscle, kidney and pancreas, as well as in many cell lines such as A549, HeLa and K562. There are two transcripts of 5 kb and 8kb present in all tissues.

Example 7: ADAMTS-R1

The nucleotide sequence of a cDNA encoding a full-length ADAMTS-R1 protein was obtained using IMAGE clone 752797 which encodes EST AA, and a human fetal brain cDNA from Clontech. RACE was performed as described above in Example 1. The nucleotide sequence, SEQ ID NO:21, of the ADAMTS-R1 cDNA and the predicted amino acid sequence, SEQ ID NO:22, of the ADAMTS-R1 protein encoded by such DNA is shown in Fig. 11.

The predicted Mr of the full-length, unprocessed ADAMTS-R1 protein is 58358.20 daltons. The domain organization of the ADAMTS-10 protein is shown in Fig. 15. In contrast to the ADAMTS-N proteins of examples 1-6, ADAMTS-R1 protein does not have a pro-metalloprotease or disintegrin-like domain or a consensus cleavage signal for furin. ADAMTS-R1 has a signal(pre) peptide which is followed by a first TS module and a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-R1 is 119 amino acids in length and is followed by 3 additional TS modules and a short sequence of 33 amino acids. The ADAMTS-R1 protein contains one potential glycosylation sites which is in the spacer domain. ADAMTS-R1 bears 30-40% sequence identity to ADAMTS1 and ADAMTS4 in the related domains. ADAMTS-R1 mRNA is present in human heart, brain, kidney, muscle, lung, placenta, testis, ovary, colon,

Although certain embodiments of this invention have been shown and described, various adaptations and modifications can be made without departing from the scope of the invention as defined in the appended claims.

CLAIMS

1. An isolated mammalian protein selected from the group consisting of an ADAMTS-5 protein an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.

2. The isolated mammalian protein of claim 1 wherein said protein comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ ID NO:14; amino acid 1 through amino acid 874 of SEQ ID NO:16; amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20; and amino acid 1 through amino acid 547 of SEQ ID NO:22.

3. The isolated protein of claim 2 wherein said amino acid sequence further comprises a prepropeptide sequence at the amino terminus thereof.

4. The isolated protein of claim 1 wherein said protein is a human ADAMTS-5 protein or a mouse ADAMTS-5 protein.

5. The isolated protein of claim 1 wherein said protein is a human ADAMTS-6 protein.

6. The isolated protein of claim 1 wherein said protein is a human

7. The isolated protein of claim 1 wherein said protein is a human

ADAMTS-9 or a mouse ADAMTS-9 protein.

9. The isolated protein of claim 1 wherein said protein is a human ADAMTS-10 or a mouse ADAMTS-10 protein.

10. The isolated protein of claim 1 wherein said protein is a human ADAMTS-R1 protein.

11. An isolated polynucleotide comprising a sequence which encodes a mammalian protein selected from the group consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS 10 protein, and an ADAMTS-R1 protein.

12. The isolated polynucleotide of claim 11 wherein said protein comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ ID NO:14; amino acid 1 through amino acid 874 of SEQ ID NO:16; amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 480 of SEQ ID NO:20; and amino acid 1 through amino acid 947 of SEQ ID NO:22.

13. The isolated polynucleotide of claim 11 wherein said nucleotide sequence encodes a protein having a signal sequence at the amino terminus thereof.

[illegible] NO:1 or an allelic variant thereof; nucleotides 1 through [illegible]

nucleotide 1519 of SEQ ID NO:3 or an allelic variant thereof; nucleotide 754 through nucleotide 2602 of SEQ ID NO:5 or an allelic variant thereof; nucleotide 708 through nucleotide 3003 of SEQ ID NO:7 or an allelic variant thereof; nucleotide 962 through nucleotide 2992 of SEQ ID NO:9 or an allelic variant thereof; nucleotide 1 through nucleotide 739 of SEQ ID NO:11 or an allelic variant thereof; nucleotide 708 through nucleotide 5648 of SEQ ID NO:13 or an allelic variant thereof; nucleotide 1 through nucleotide 2625 of SEQ ID NO:15 or an allelic variant thereof; nucleotide 634 through nucleotide 3243 of SEQ ID NO:17 or an allelic variant thereof; nucleotide 1 through nucleotide 1642 of SEQ ID NO:19 or an allelic variant thereof; and nucleotide 51 through nucleotide 1625 of SEQ ID NO:21 or an allelic variant thereof.

15. The isolated polynucleotide of claim 11 wherein said polynucleotide hybridizes under stringent conditions to a nucleic acid molecule comprising a sequence complementary to the protein encoding sequence of SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7; SEQ ID NO:9; SEQ ID NO:11; SEQ ID NO:13; SEQ ID NO:15; SEQ ID NO:17; SEQ ID NO:19; or SEQ ID NO:21.

16. An isolated polynucleotide having a sequence which is complementary to the protein encoding sequence of the polynucleotide of claim 11.

17. An expression vector comprising a polynucleotide of claim 11.

18. A host cell transformed or transfected with an expression vector of claim 17.

19. A process for expression of an ADAMTS-1 protein in an ADAMTS-1

protein; and

(b) recovering said ADAMTS-N protein or said ADAMTS-R1 protein from the host cell culture.

20. An antibody that binds to a protein selected from the group consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein and an ADAMTS-R1 protein.

21. An oligopeptide for producing an antibody that binds to an ADAMTS N protein or an ADAMTS-R1 protein wherein said oligopeptide has a sequence selected from the group consisting of:

a) SVSIERFVETLVVADK, SEQ ID NO:23;

b) EVAEAANFLALRSEDPDKY, SEQ ID NO:24;

c) VKEDVENPKAVVDGDWGP, SEQ ID NO:25;

d) QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26;

e) PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27;

f) QELEEGAAVSEEPS, SEQ ID NO:28;

g) YYPENIKPKPKLQE; SEQ ID NO:29;

h) HIKVRQFKAKDQTRF; and

i) CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO:30.

Fig. 1

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Fig. 2

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Fig. 3

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Fig. 3 (con't)

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Fig. 4

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Fig. 5A

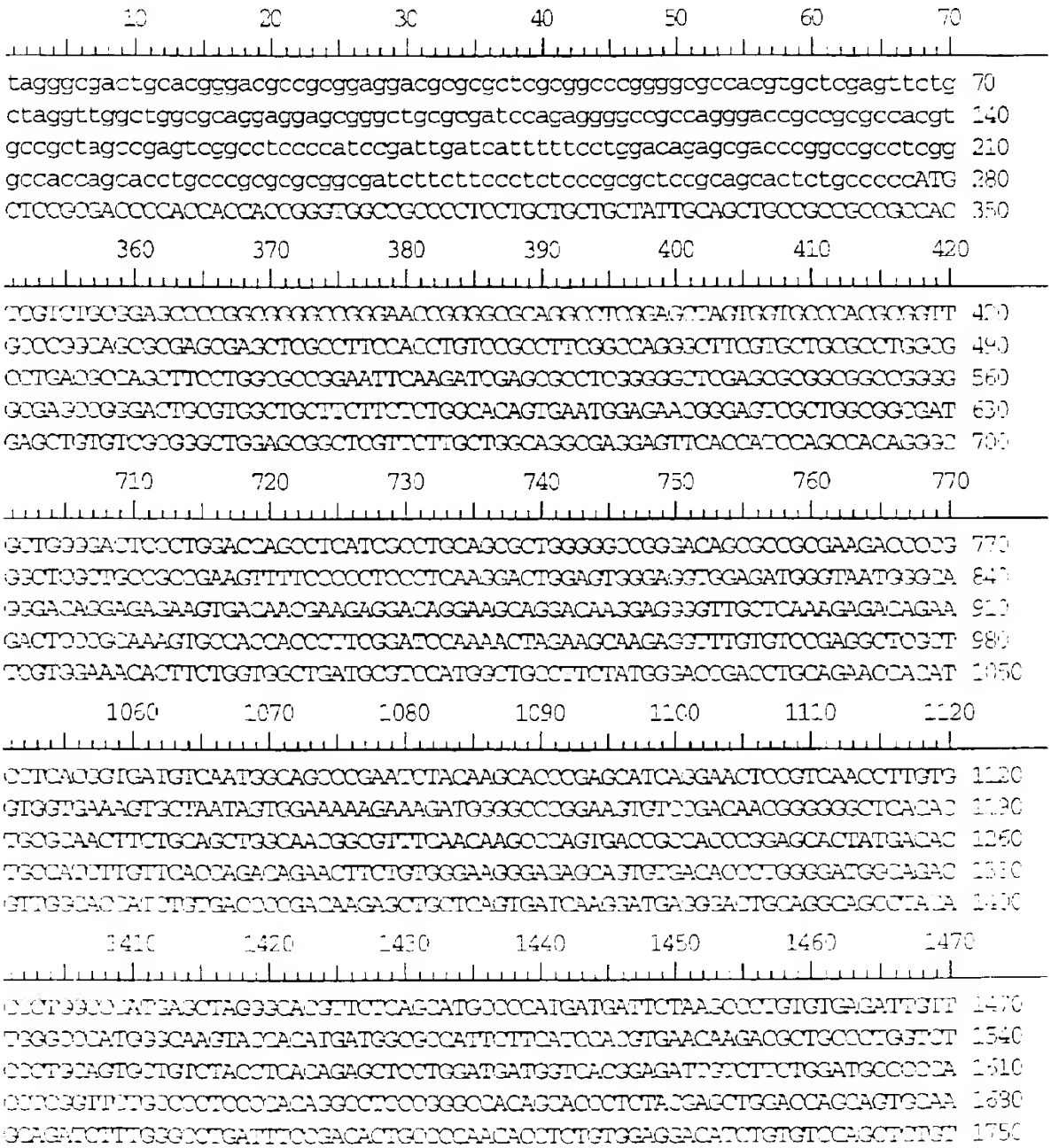
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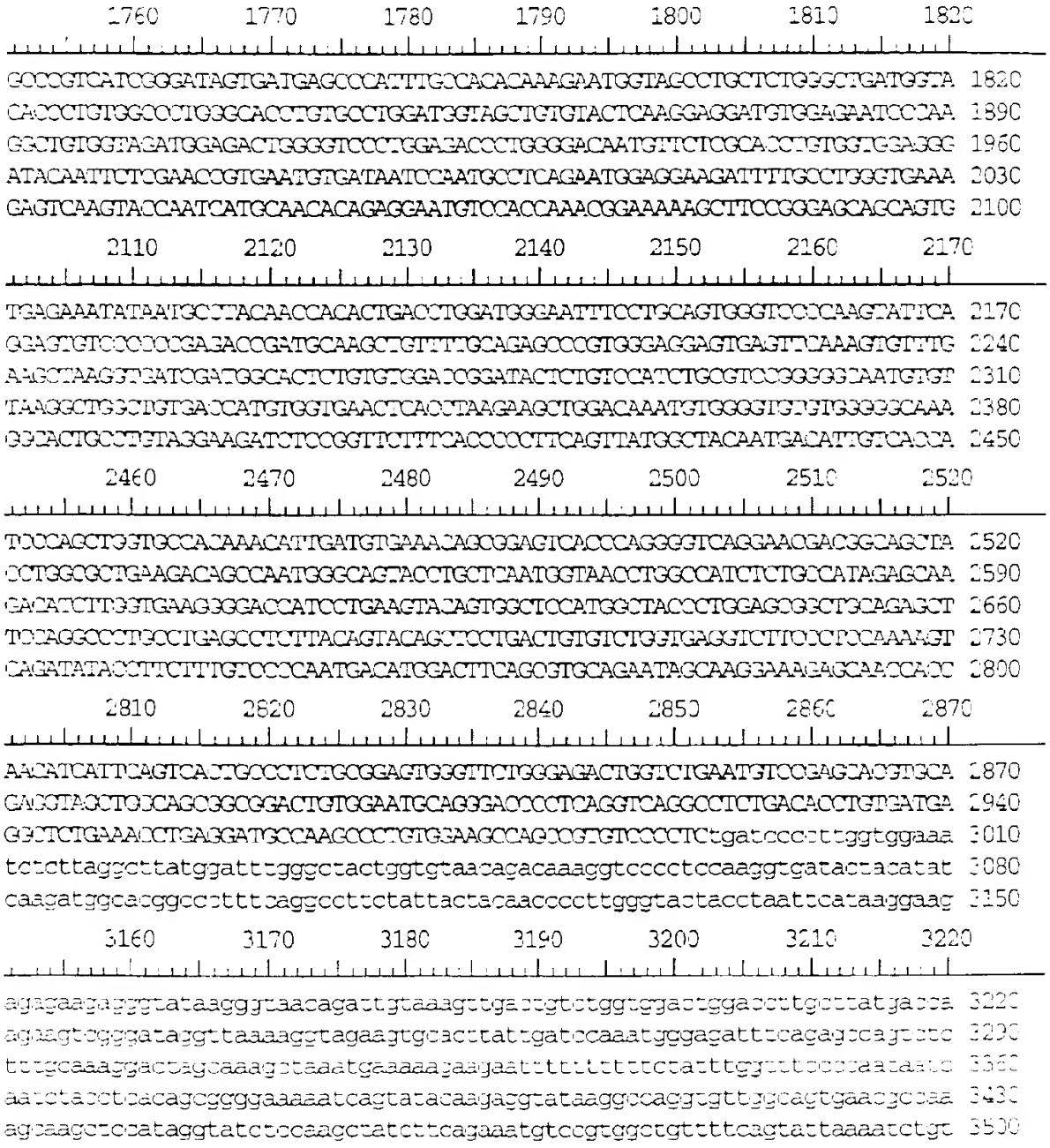
Fig. 5A (con't)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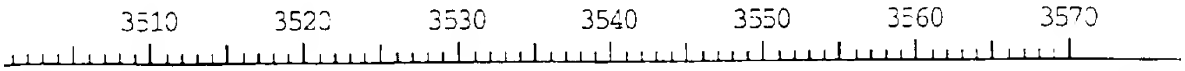

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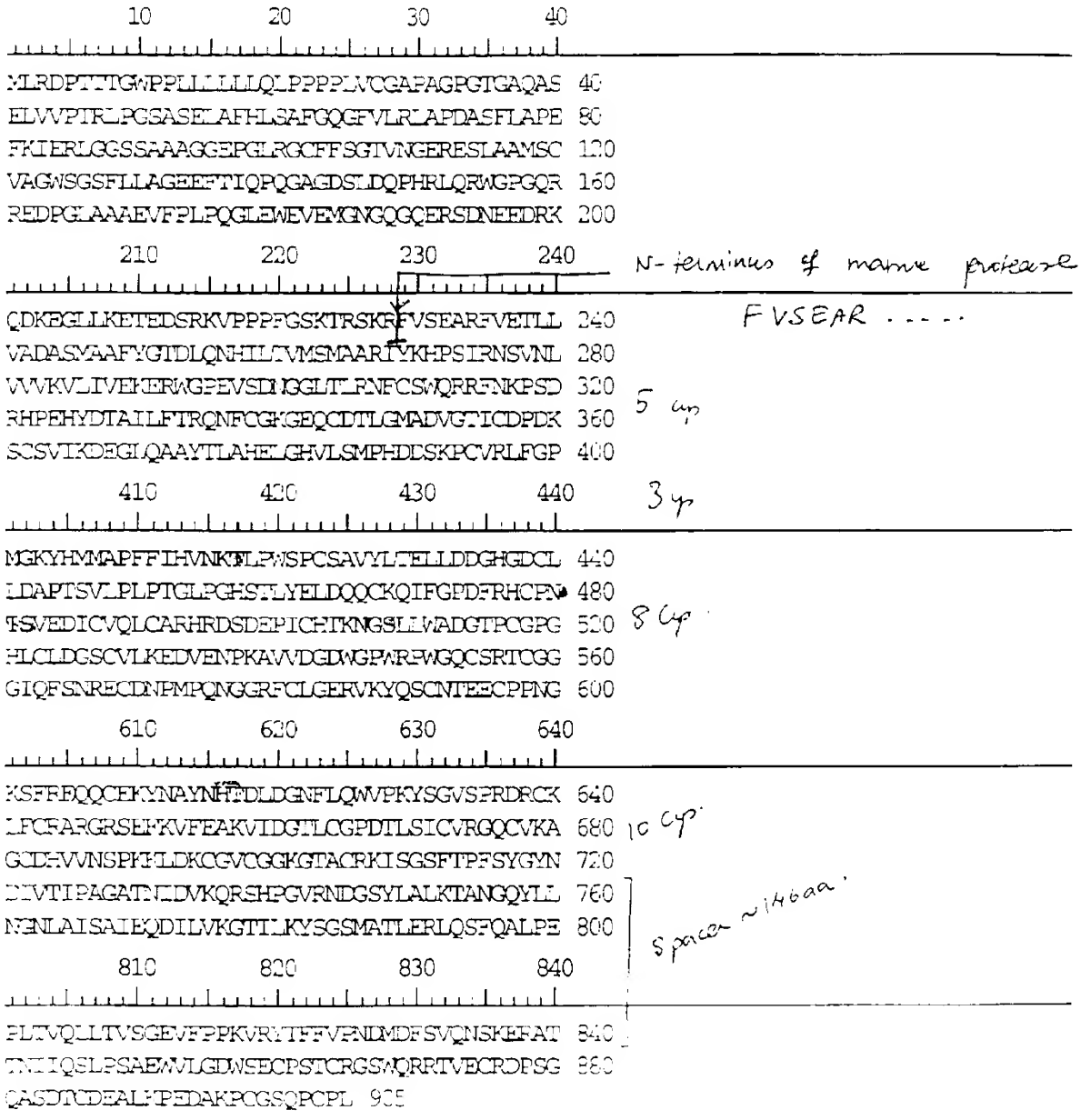
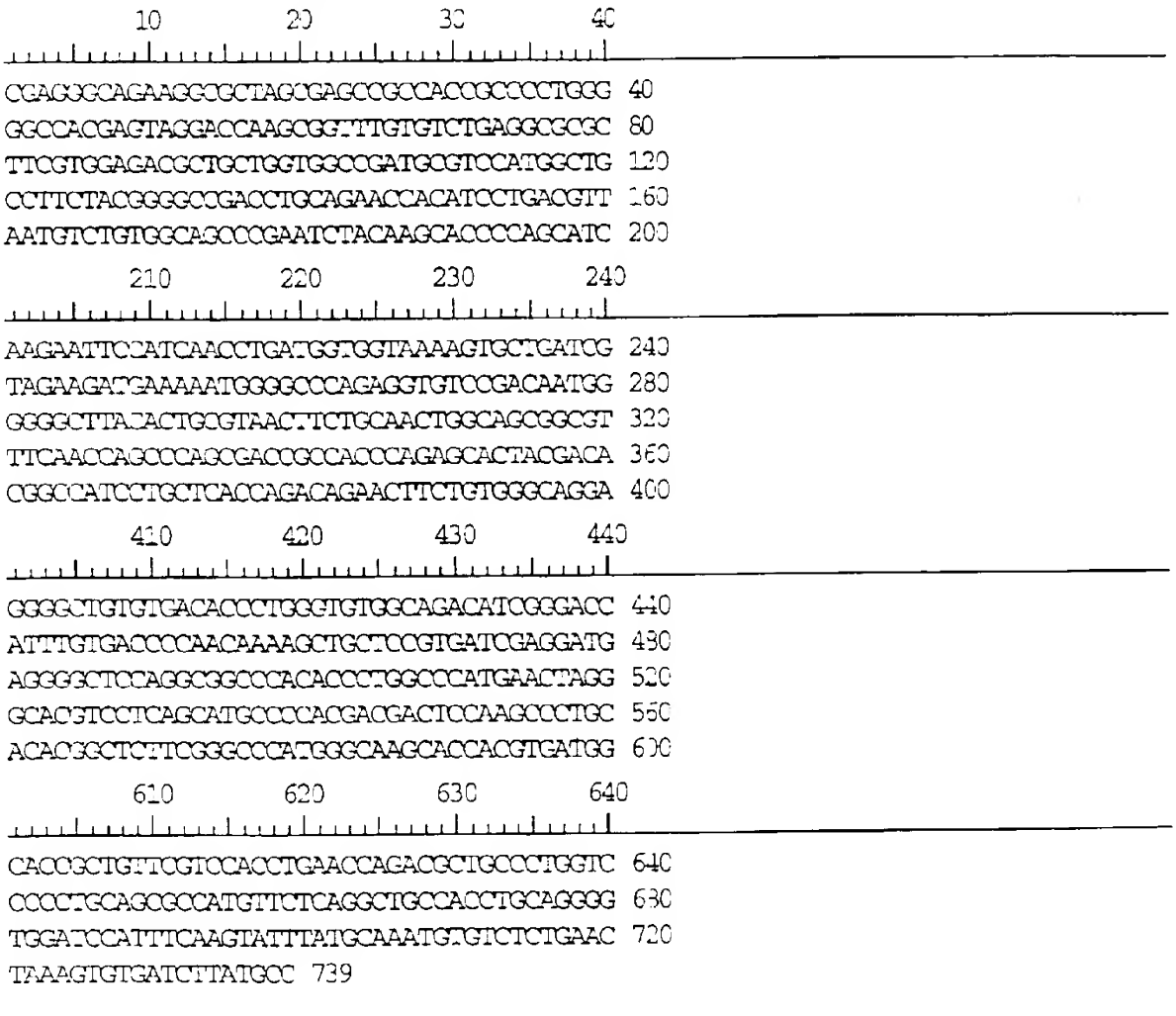


Fig. 6A

CATALYTIC DOMAIN, ADAM TS-8 (HUMAN)



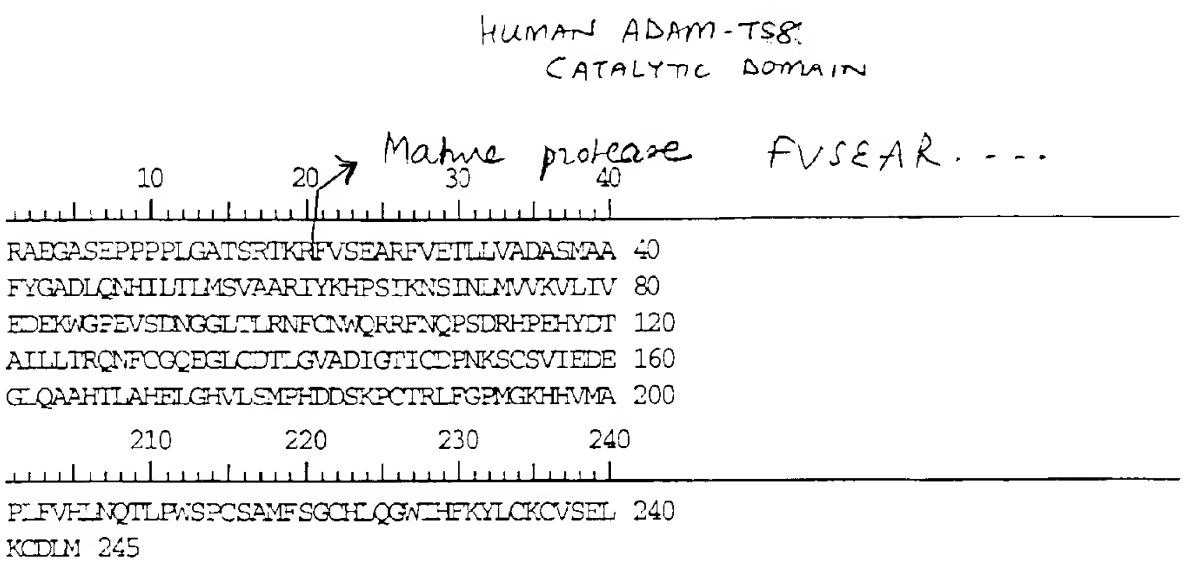

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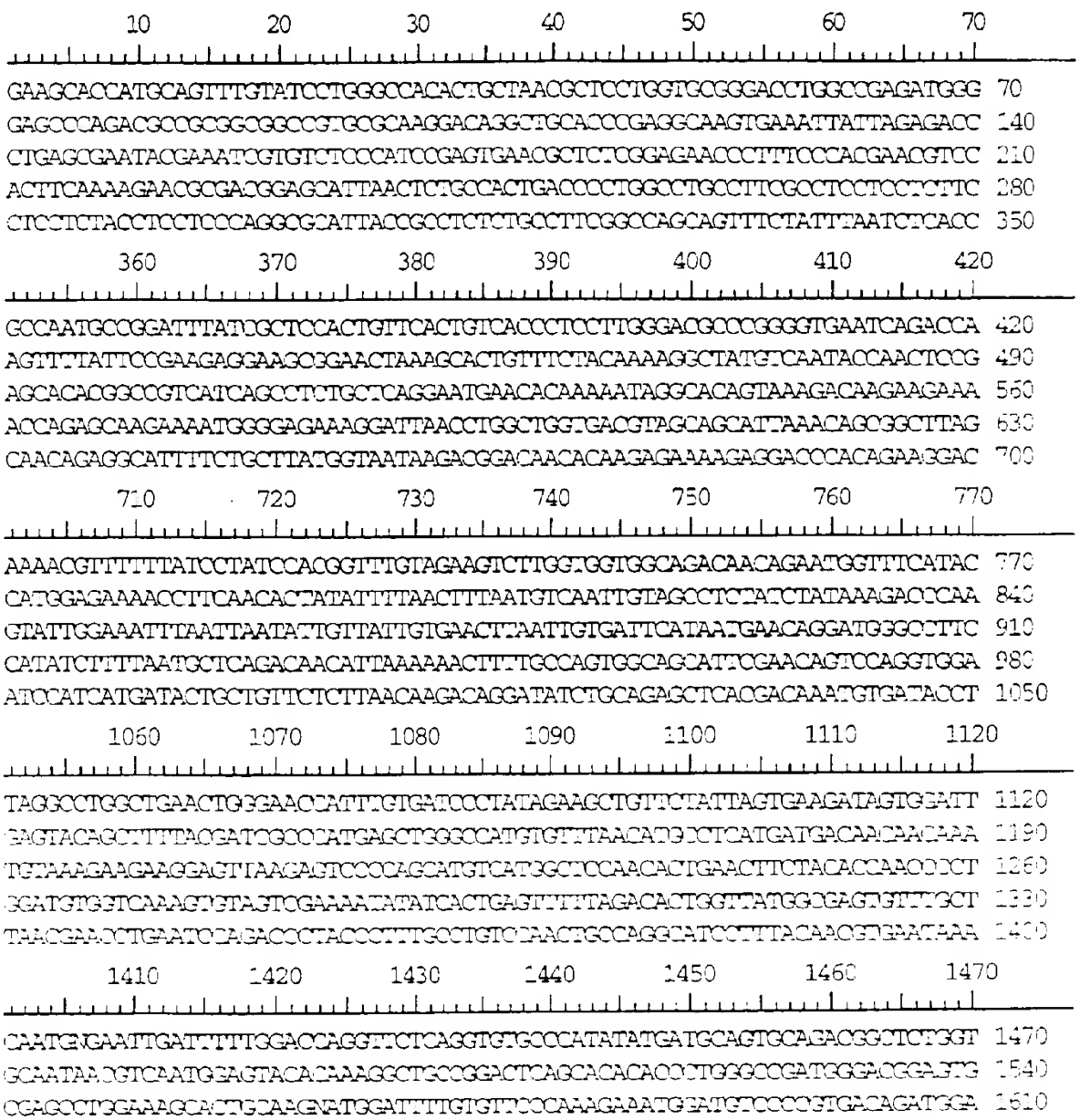
Fig. 6B

Fig. 7A

Human HDAC-T19



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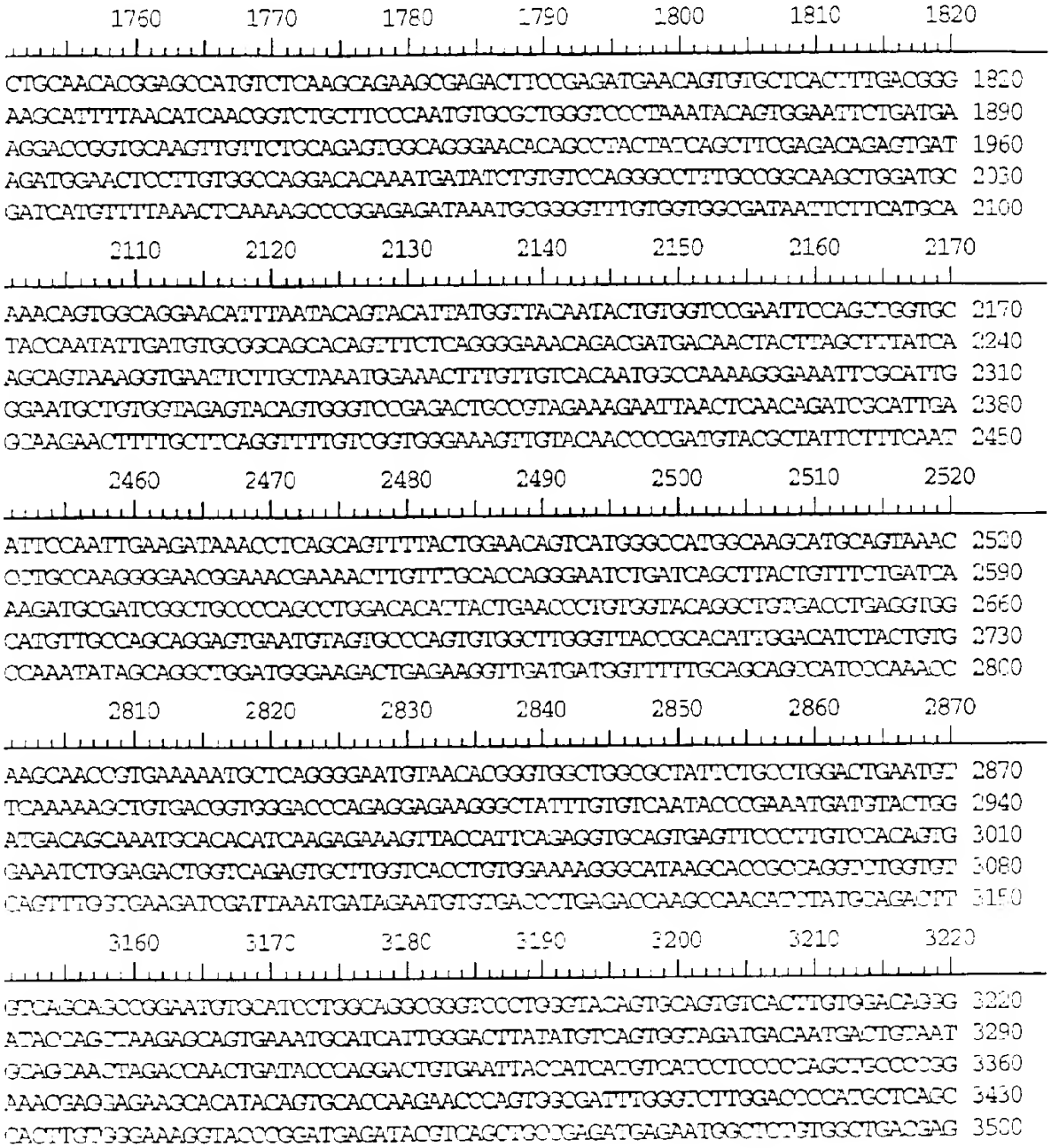
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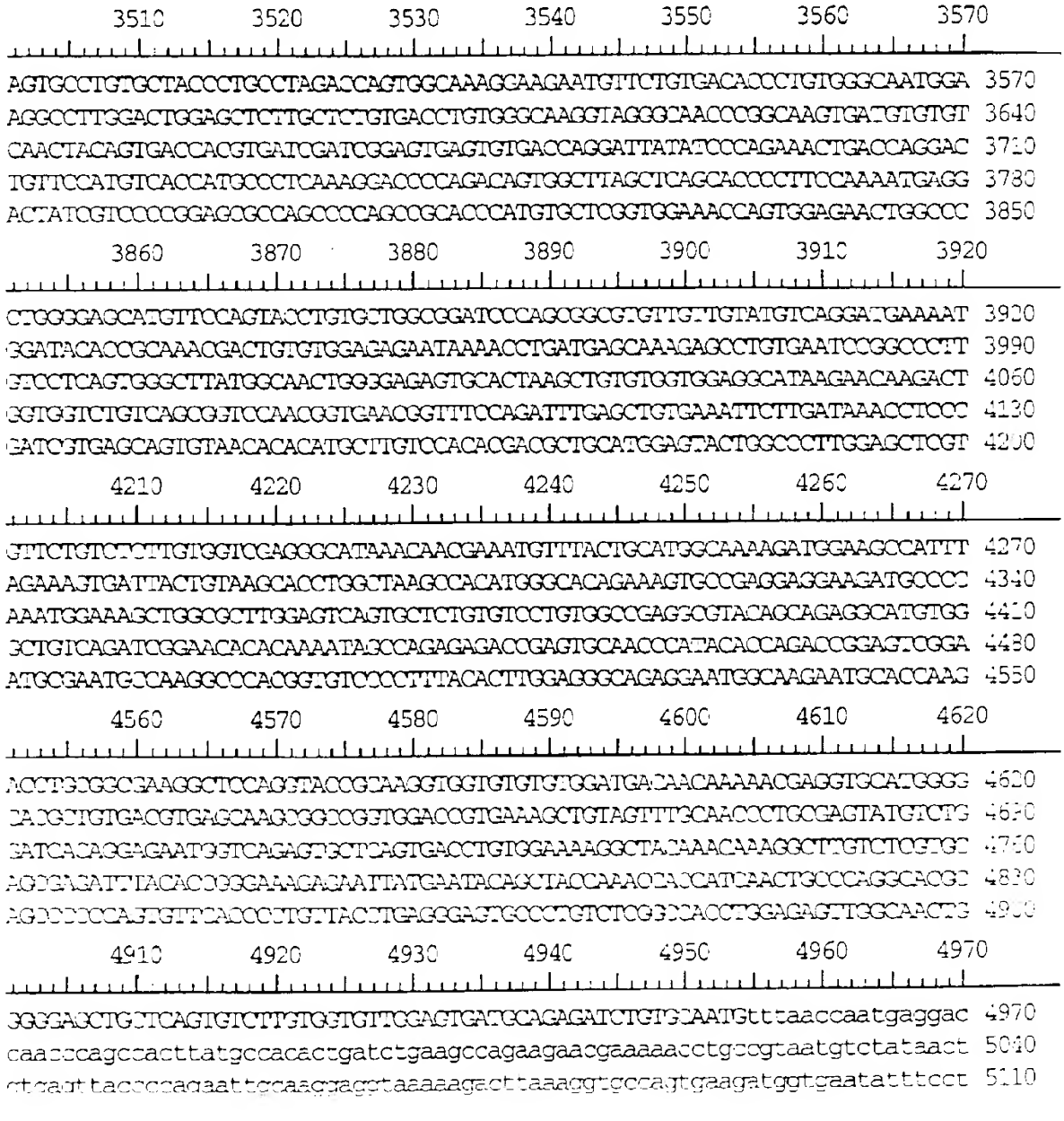
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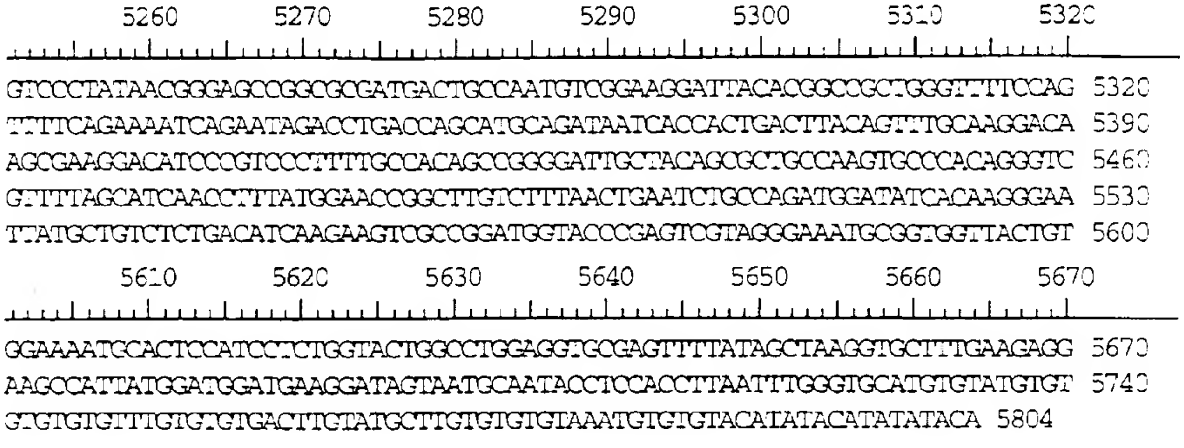
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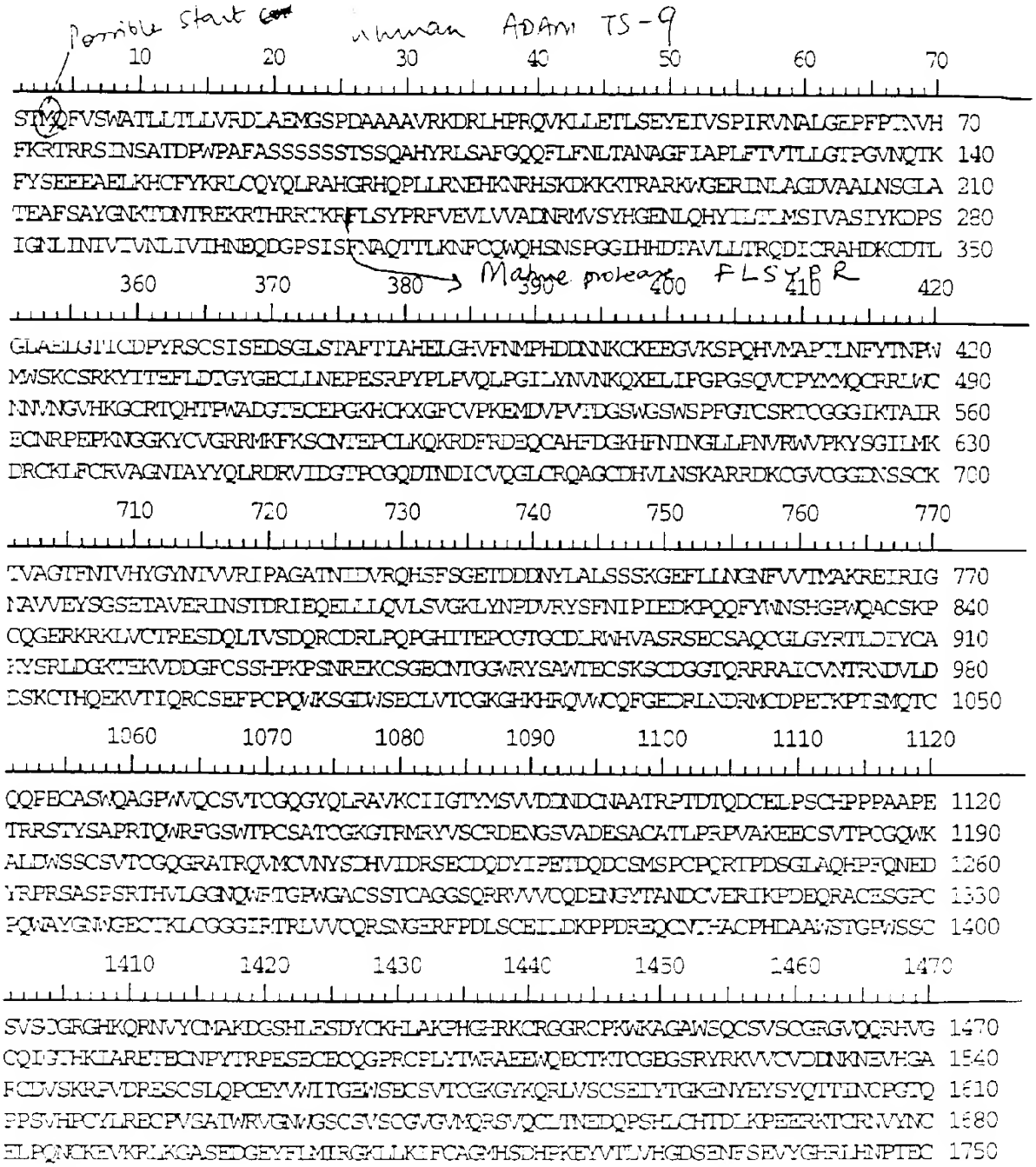
Fig. 7B



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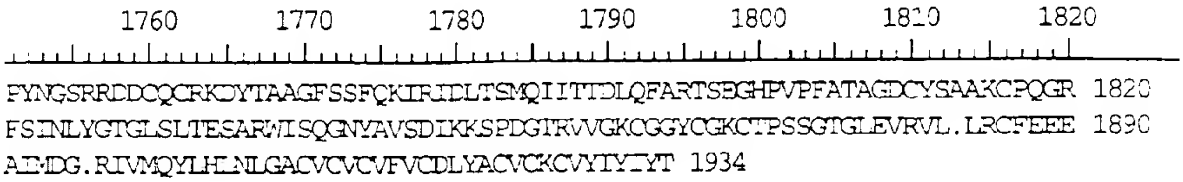
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Fig. 8

ORF=2 protein

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Mouse ADAM-TS9
FLSYPRF...
Mouse ADAM-TS9
partial segment
(see figure)

Created: Saturday, April 10, 1999 11:40 AM

DNA

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Fig. 8 (con't)

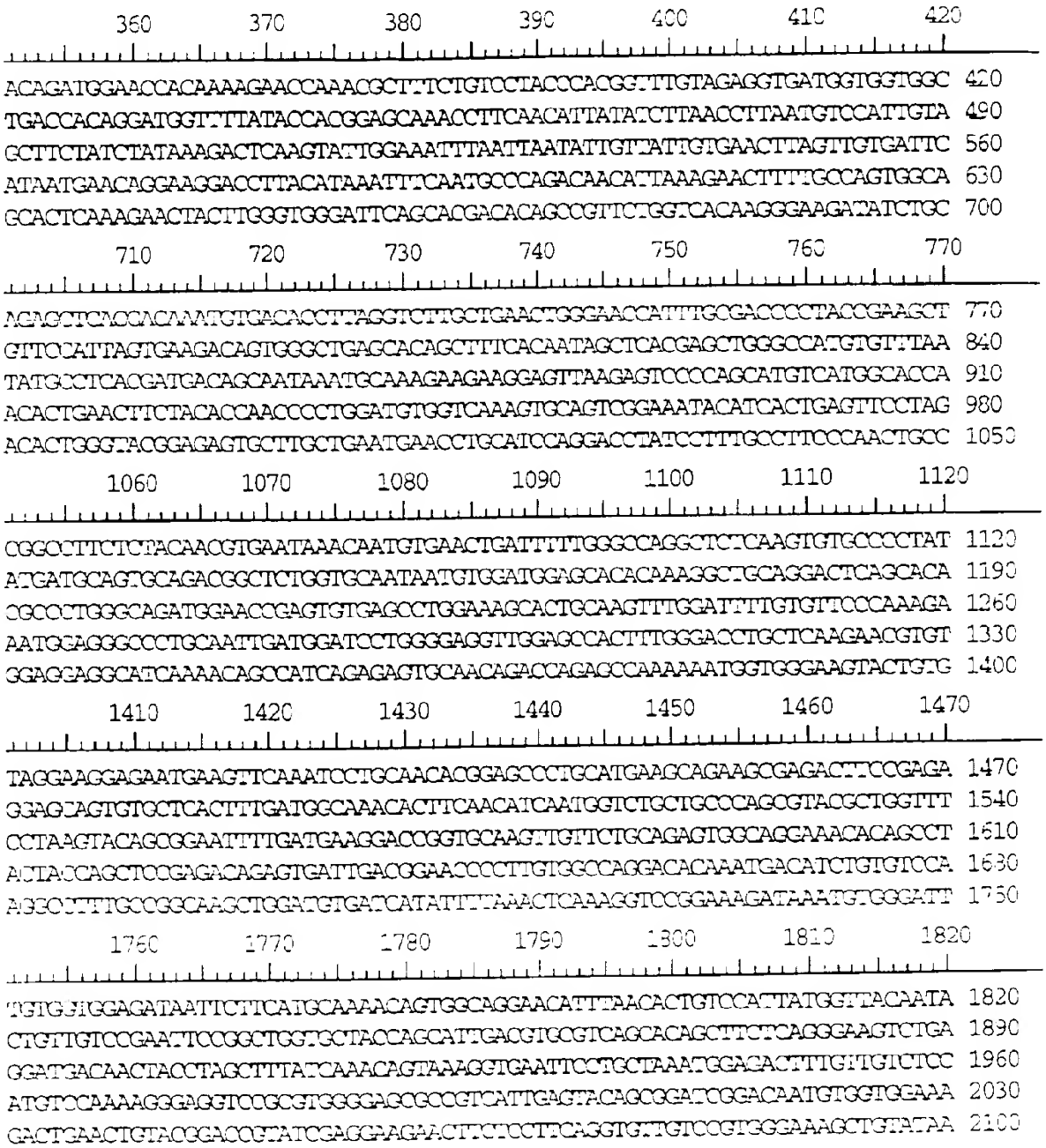
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Fig. 8 (con't)

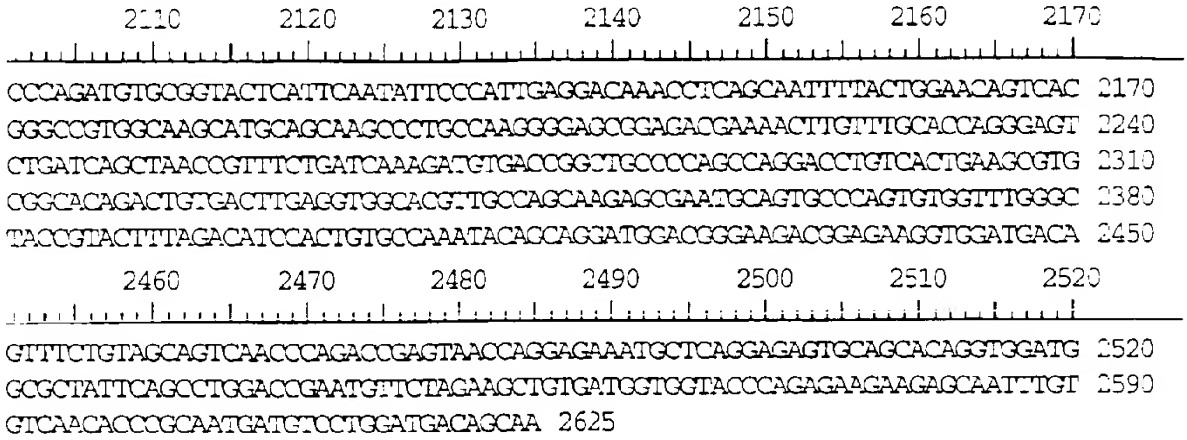
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Fig. 9A

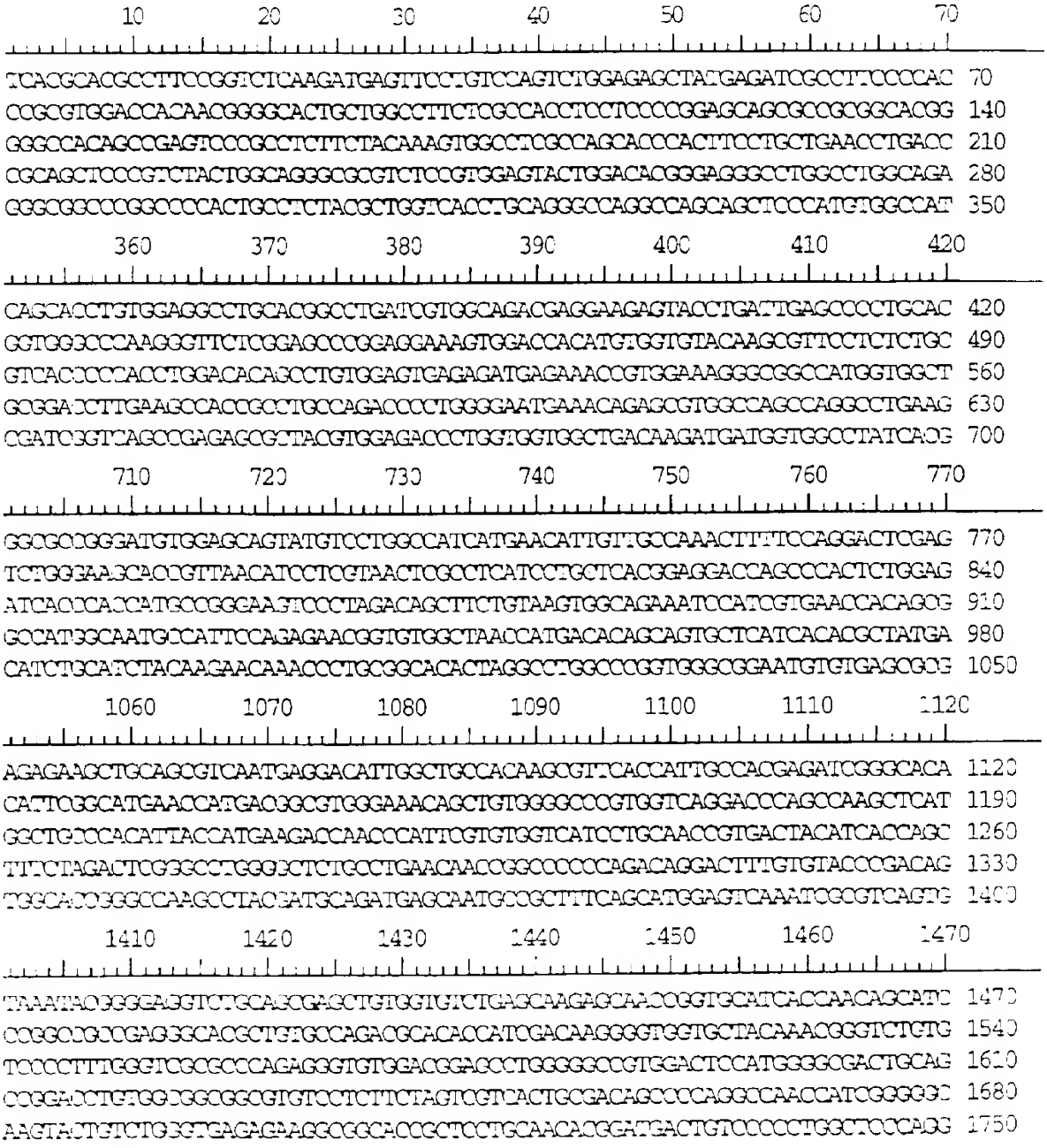
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Fig. 9A (con't)

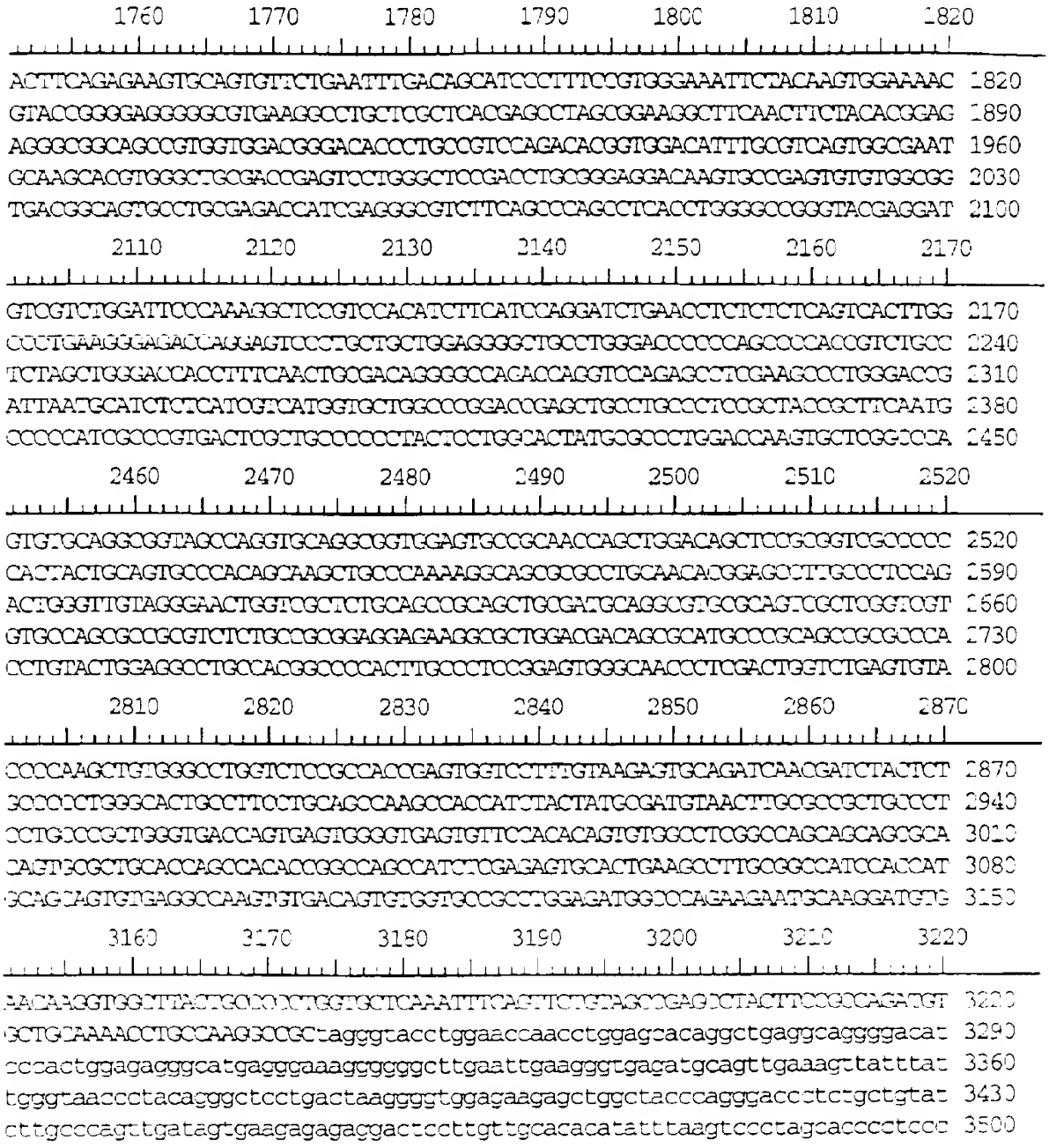
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Fig. 9A (con't)

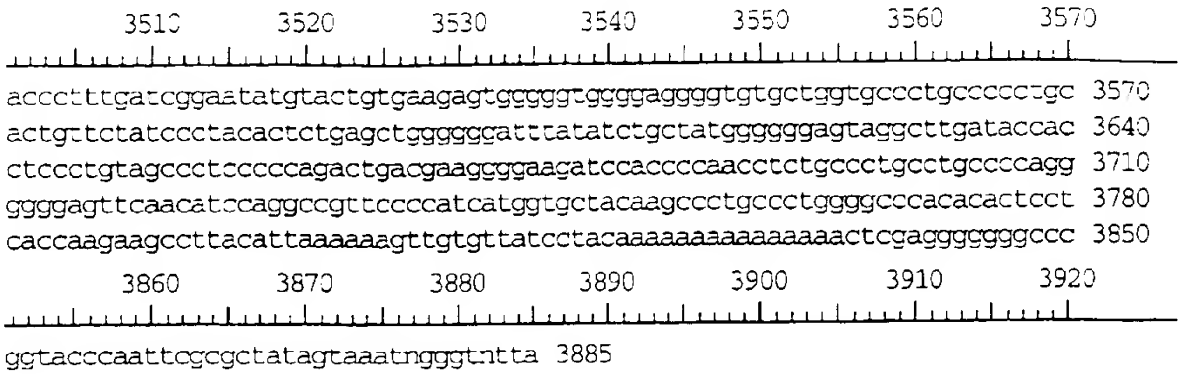
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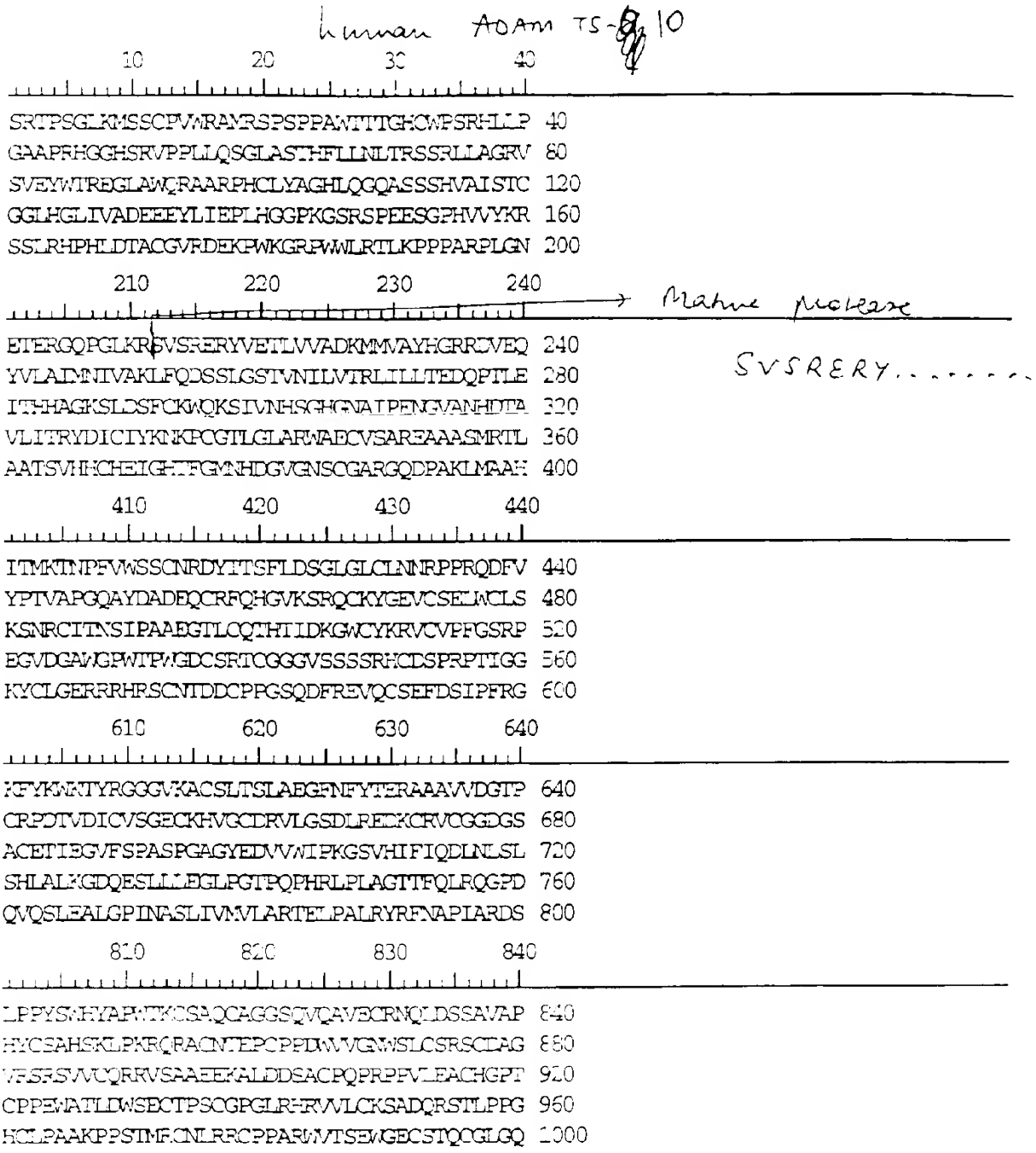
Fig. 9B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Mature protease
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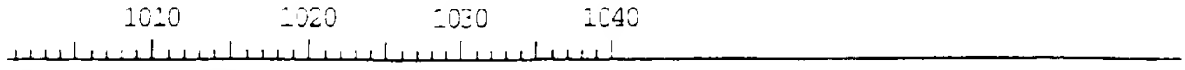

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Fig. 10A

partial sequence of mouse ADAM TS-10 (see figure)

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Fig. 10A (con't)

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GN 1642
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Fig. 10B

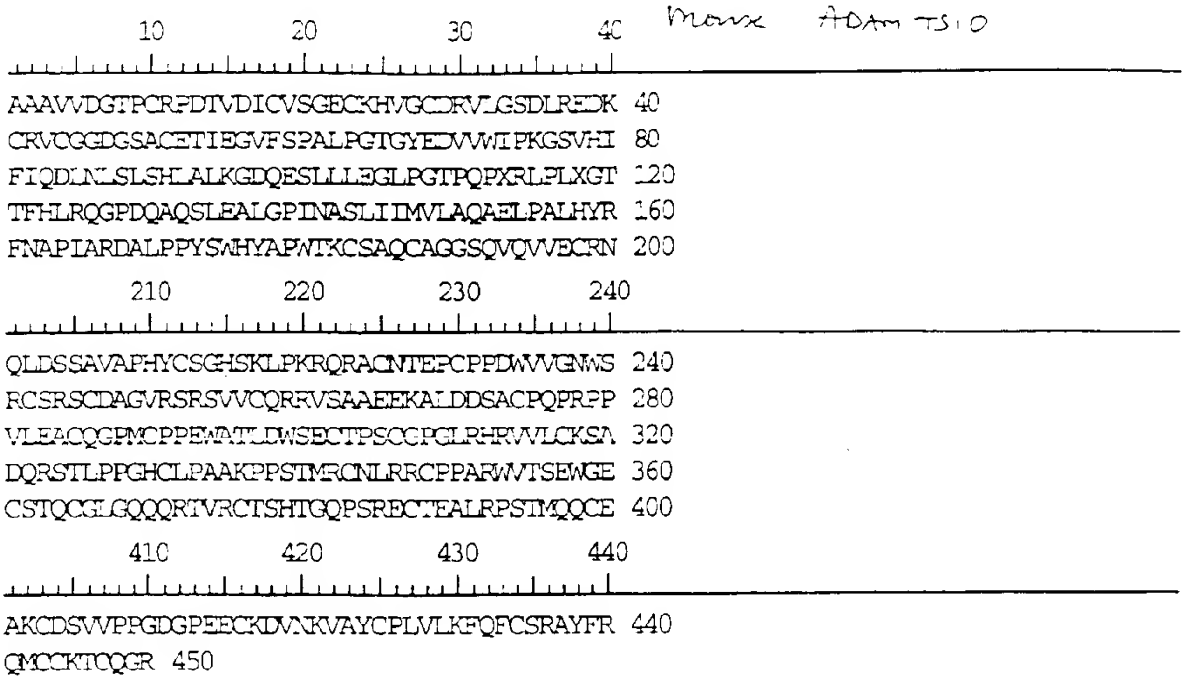
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Fig. 11A

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I)
Cloning site:5';Eco RI 3';Not I Vector; PI7T3 pac.

You can put this construct to pcDNA3.1(+) for transfection
5'-UTR is 50bp &3'-UTR is 175bp

210-215; in 482392 it's TCCTAC(SY).

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CGCAACCAAATCGGATGATACTGTGGTTGCAATTCCCTAT 680
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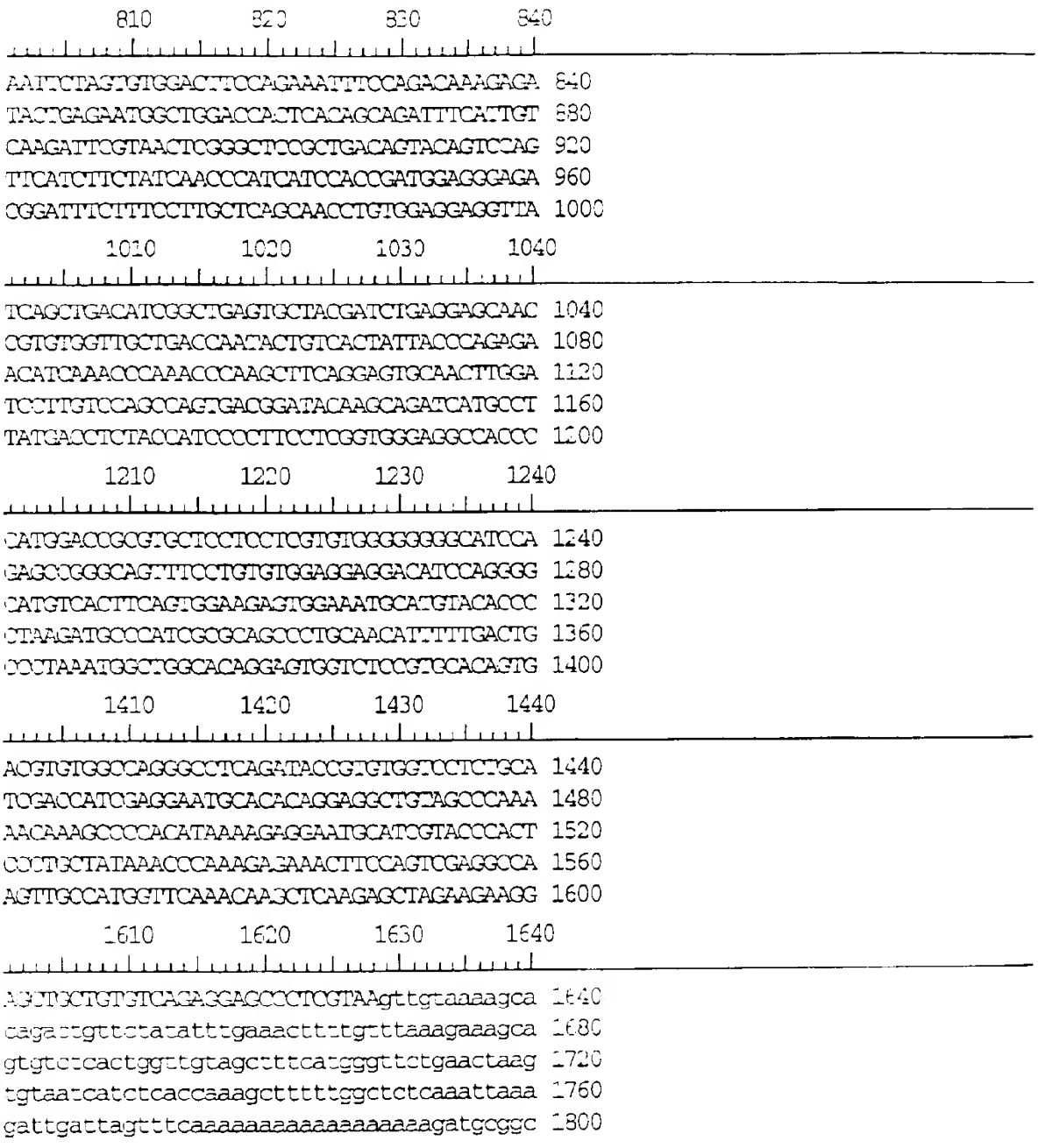
ACTTATATCTGGAAACCAAAACCCTCCAGGGGACTAAAGG 760
```

Fig. 11A (con't)


810 820 830 840
AATTCTAGTGTGGACTTCCAGAAATTTCCAGACAAAGAGA 840
TACTGAGAATGGCTGGACCACTCACAGCAGATTTCATTGT 880
CAAGATTCGTAACTCGGGCTCCGCTGACAGTACAGTCCAG 920
TTCATCTTCTATCAACCCATCATCCACCGATGGAGGGAGA 960
CGGATTTCTTTCCTTGCTCAGCAACCTGTGGAGGAGGTTA 1000
1010 1020 1030 1040
TCAGCTGACATCGGCTGAGTGCTACGATCTGAGGAGCAAC 1040
CGTGTGGTTGCTGACCAATACTGTCACTATTACCCAGAGA 1080
ACATCAAACCCAAACCCAAGCTTCAGGAGTGCAACTTGGA 1120
TCCTTGTCCAGCCAGTGACGGATACAAGCAGATCATGCCT 1160
TATGACCTCTACCATCCCCTTCCTCGGTGGGAGGCCACCC 1200
1210 1220 1230 1240
CATGGACCGCGTGCTCCTCCTCGTGTGGGGGGGGCATCCA 1240
GAGCCGGGCAGTTCCTGTGTGGAGGAGGACATCCAGGGG 1280
CATGTCACTTCAGTGGAAGAGTGGAAATGCATGTACACCC 1320
CTAAGATGCCCATCGCGCAGCCCTGCAACATTTTTGACTG 1360
CCCTAAATGGCTGGCACAGGAGTGGTCTCCGTGCACAGTG 1400
1410 1420 1430 1440
ACGTGTGGCCAGGGCCTCAGATACCGTGTGGTCCTCTGCA 1440
TCGACCATCGAGGAATGCACACAGGAGGCTGTAGCCCAAA 1480
AACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACT 1520
CCCTGCTATAAACCCAAAGAGAAACTTCCAGTCGAGGCCA 1560
AGTTGCCATGGTTCAAACAAGCTCAAGAGCTAGAAGAAGG 1600
1610 1620 1630 1640
AGCTGCTGTGTCAGAGGAGCCCTCGTAAgttgtaaaagca 1640
cagactgtttctatatttgaaactttgtttaaagaaagca 1680
gtgtctcactggttgtagctttcatgggttctgaactaag 1720
tgtaatcatctcaccaaagcttttggctctcaaattaaa 1760
gattgattagtttcaaaaaaaaaaaaaaaaaagatgcggc 1800

g. 11A (con't)

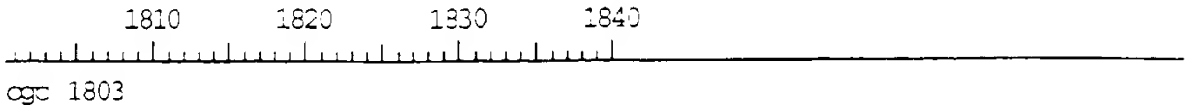


Fig. 11B

---	Asp(D)	30	# cua	Leu(L)	3	# uca	Ser(S)	6	# guu	Val(V)	6
ugc	Cys(C)	26	# cuc	Leu(L)	11	# ucc	Ser(S)	10	# ---	Val(V)	29
ugu	Cys(C)	10	# cug	Leu(L)	14	# ucg	Ser(S)	5	# nnn	???(X)	0
---	Cys(C)	36	# cuu	Leu(L)	6	# ucu	Ser(S)	5	# TOTAL		526
caa	Gln(Q)	7	# uua	Leu(L)	4	# ---	Ser(S)	43	#		

Created: Wednesday, May 5, 1999 10:19 AM

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I)
Cloning site:5';Eco RI 3';Not I Vector; PT7T3 pac.

...

human ADAM-TSR1

Adam-TS related protein-1.

```
         10        20        30        40
         |         |         |         |
MECCRRATPGTLLLFLAFLLLSSRTARSEEDRDGLWDAWG 40
PWSECSRTCGGGAANSLPRCLSSKSCEGRNIRYRTCSNVD 80
CPPEAGDFRAQQCSAHNDVKHHGQFYEWLPVSNDFDNPCS 120
LKCQAKGTTLVVELAPKVLDGTRCYTESLDMCISGLCQIV 160
GCDHQLGSTVKEDNCGVCNGDGSTCRLVRGQYKSQLSATK 200
         210       220       230       240
         |         |         |         |
SDDTVVAIPYGSRHIRLVLKGPDHLYLETKTLQGTKGENS 240
LSSTGTFLVDNSSVDFQIFPDKEILRMAGPLTADFIVKIR 280
NSGSADSTVQFIFYQPIIHRWRETDFFPCSATCGGGYQLT 320
SAECYDLRSNRVVADQYCHYYPENIKPKPKLQECNLDPCP 360
ASDGYKQIMPYDLYHPLPFWEATPWTACSSSCGGGIQSRA 400
         410       420       430       440
         |         |         |         |
VSCVEEDIQGHVTSVEENKCMYTPKVPIAQPCNIFDCPKW 440
LAQEWSPCTVTCGQGLRYRVVLCIDHRGMHTGCCSPKTKP 480
HIKEECIVPTPCYKPKEPLPVEAKLPWFKQAQELEEGAAV 520
SEEPS. 526
```

Signal peptide

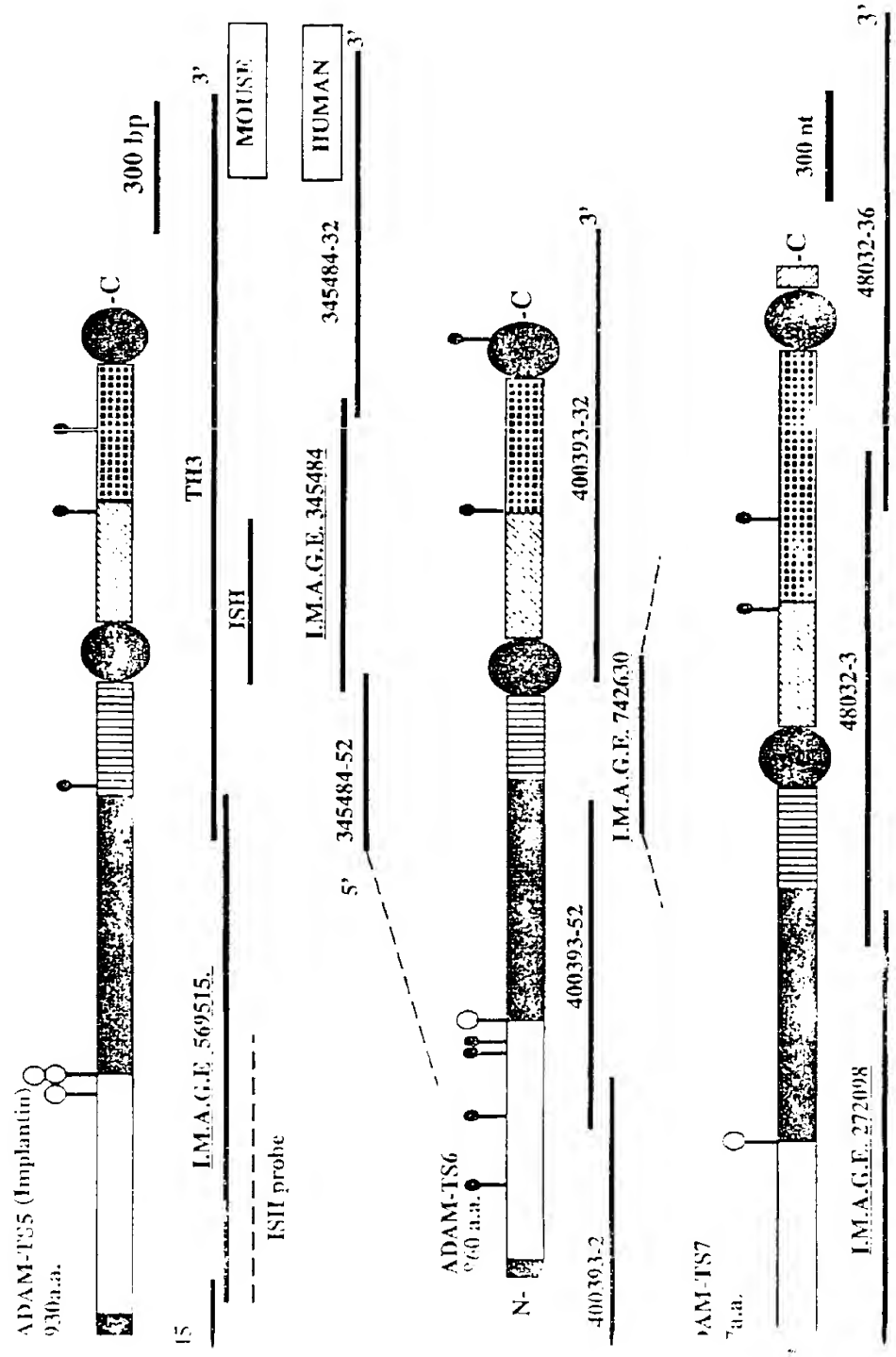
(C) YYPENIKPKPKLQE

(C) QELEEGAAV

C- terminal epitope for Ab

Similar to ADAM-TS family but lacks the prometalloprotease and disintegrin domain. Can [illegible] this may be a inhibitor of the

Fig. 12


ADAM-TS5 (Implantin)
930a.a.
-C
300 bp
3'
MOUSE
HUMAN
TH3
I.M.A.G.E. 569515
ISH
ISH probe
I.M.A.G.E. 345484
345484-32
5'
345484-52
ADAM-TS6
960 a.a.
N-
-C
400393-32
3'
400393-52
400393-2
I.M.A.G.E. 742630
ADAM-TS7
-C
300 nt
48032-3
48032-36
I.M.A.G.E. 272098
3'

a

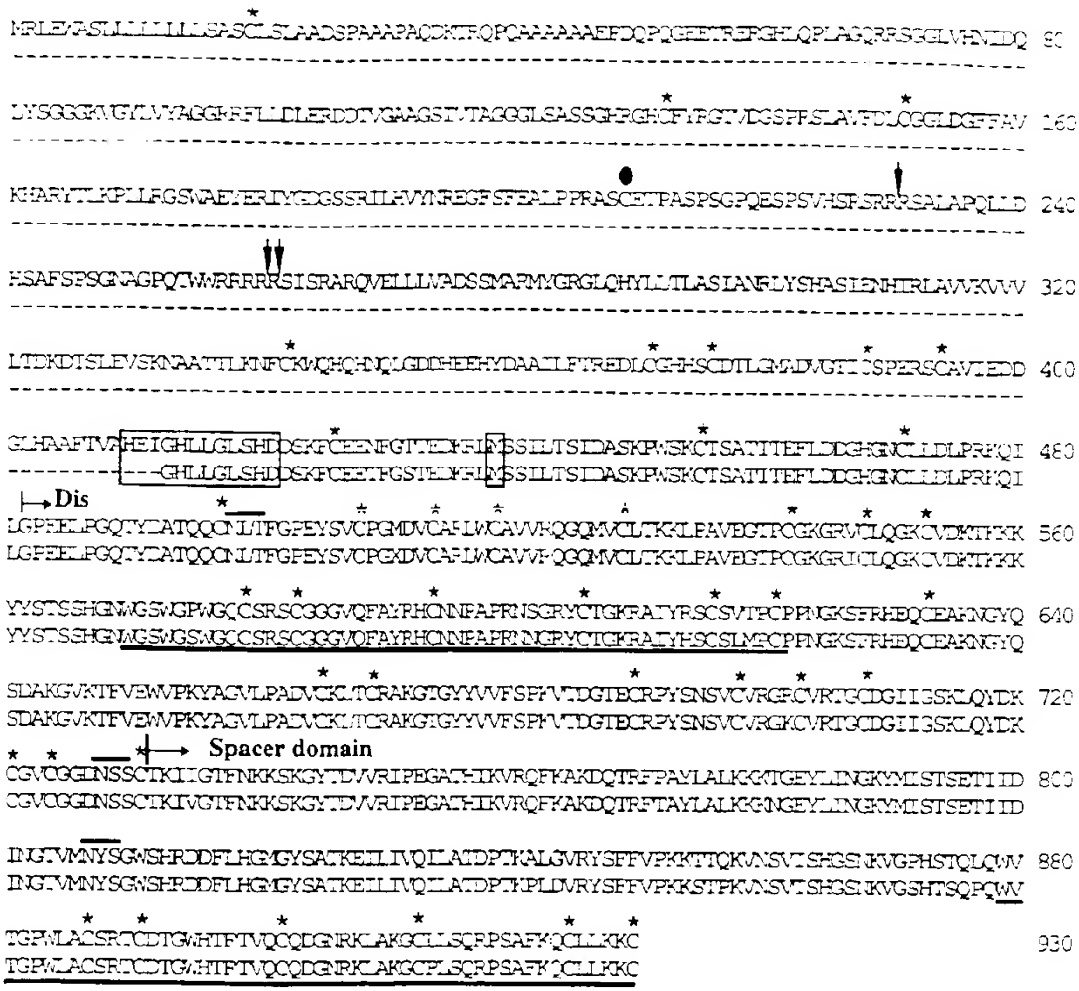
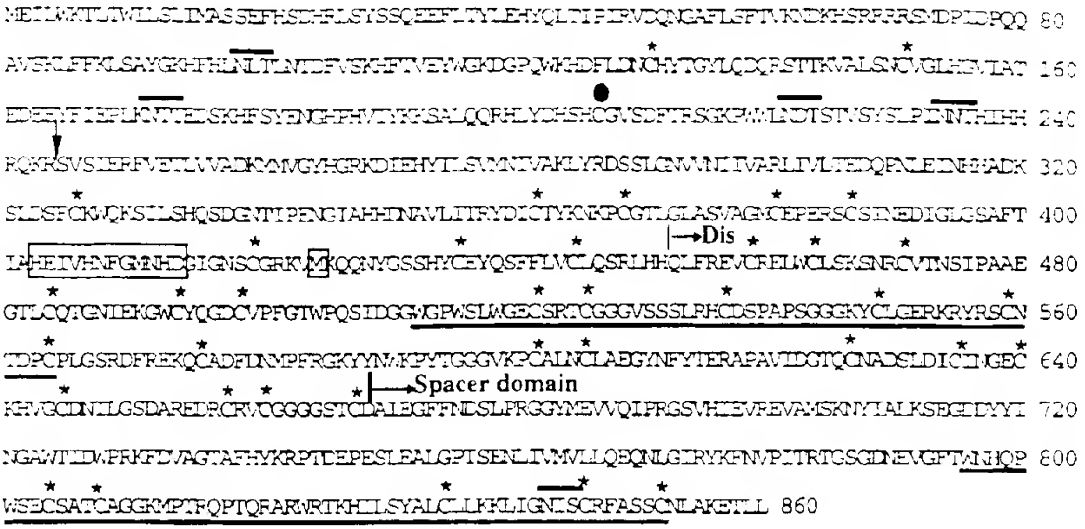


Fig. 13

Hurska nen et al^, Fig. 2a



C

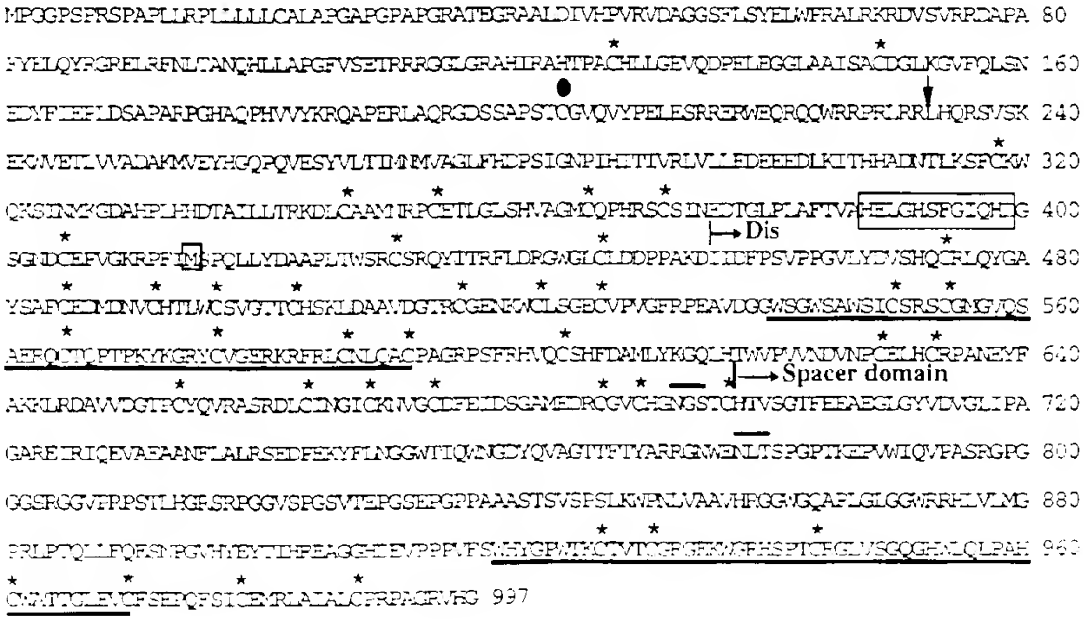


Fig. 13 (con't)

a

adamalysin II	HELGHNLGMEHD
atrolysin A	HELGHNLGMVHD
hADAM-9	HELGHNLGMNHD
hADAM-10	HEVGHNFGSPHD
hADAM-15	HELGHSLGLDHD
hADAM-17	HELGHNFGAEHD
mADAM-19	HEIGHNFGMSHD
mADAM-TS1	HELGHVFNMPHD
hADAM-TS2	HETGHVLGMEHD
hADAM-TS3	HETGHVLGMEHD
hADAM-TS4	HELGHVFNMLHD
mADAM-TS5	HEIGHLLGLSHD
hADAM-TS6	HEIVHNFGMNHD
hADAM-TS7	HELGHSFGIQHD

b

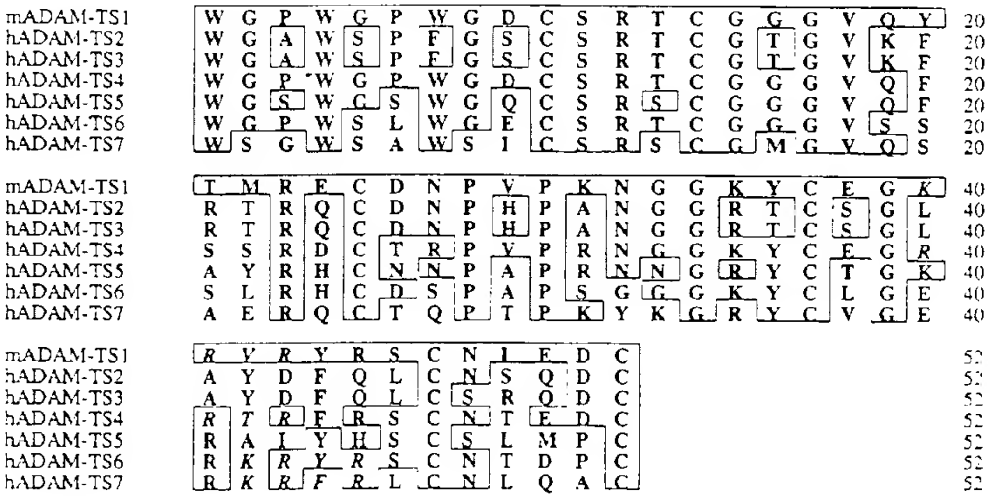


Fig. 13 (con't)

Fig. 14

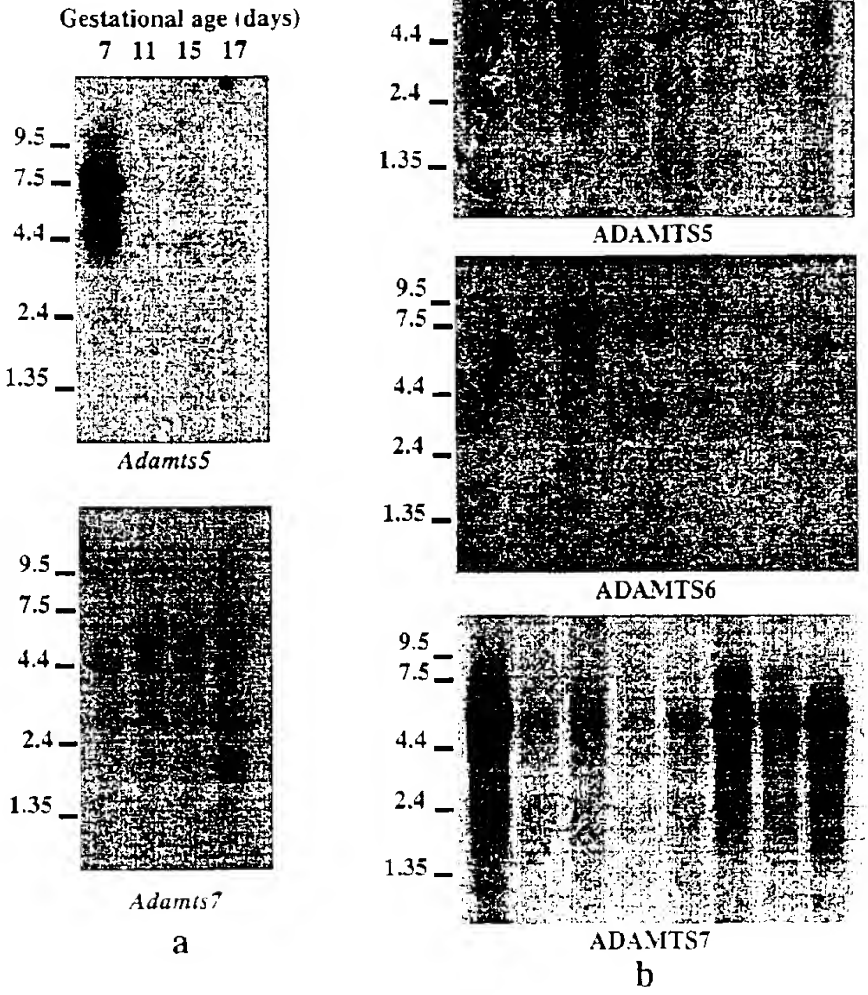

Gestational age (days)
7 11 15 17
9.5
7.5
4.4
2.4
1.35
Adamts5
Adamts7
a
Heart
Brain
Placenta
Lung
Liver
Skeletal muscle
Kidney
Pancreas
ADAMTS5
ADAMTS6
ADAMTS7
b

Fig. 15

ADAM-TS RELATED PROTEIN-1 (ADAM-TSR1)

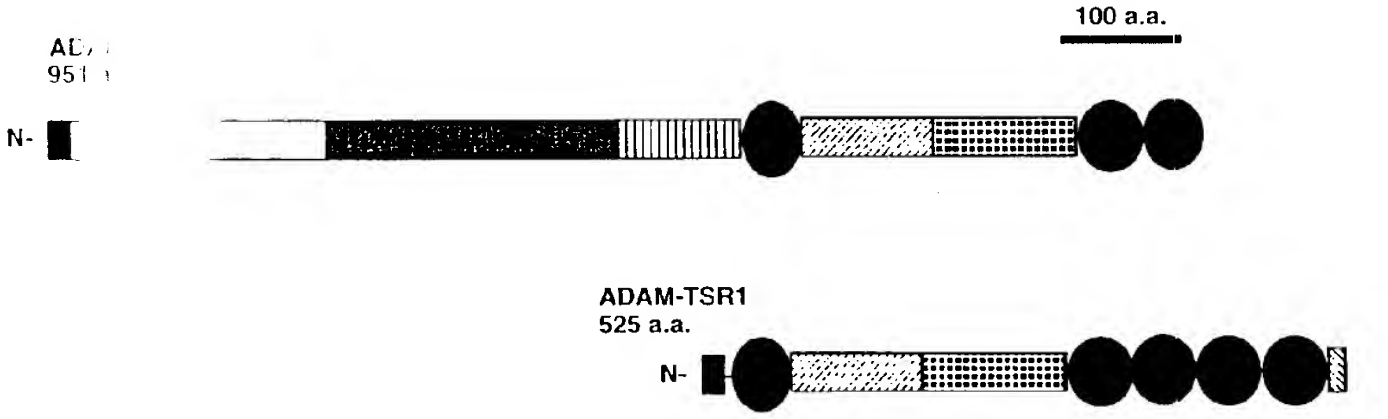


Fig. 15 (con't)

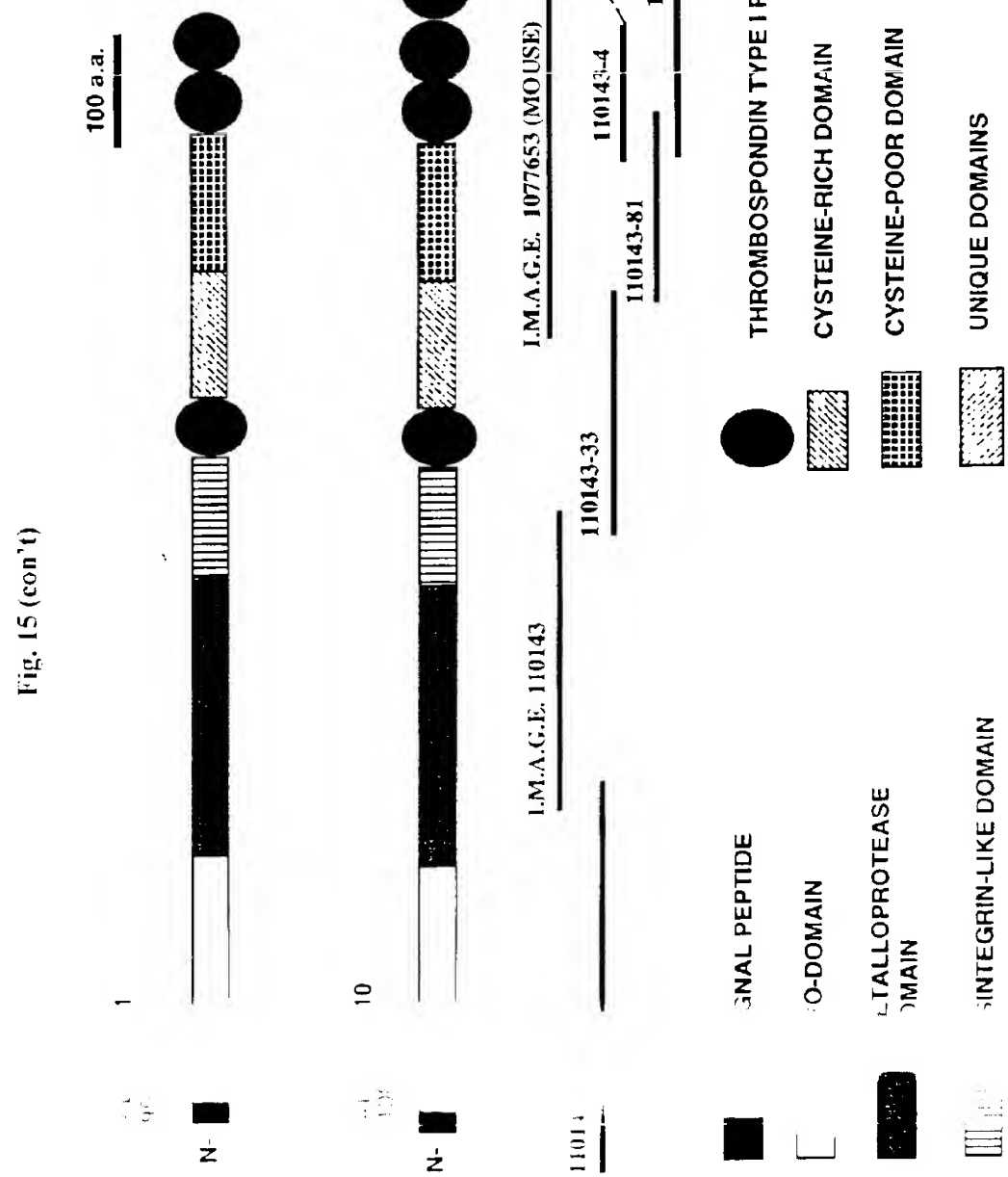

100 a.a.
1
10
N-
N-
I.M.A.G.E. 110143
110143-33
I.M.A.G.E. 1077653 (MOUSE)
110143-81
110143-4
110143-15
SIGNAL PEPTIDE
PRO-DOMAIN
METALLOPROTEASE DOMAIN
INTEGRIN-LIKE DOMAIN
THROMBOSPONDIN TYPE I REPEAT
CYSTEINE-RICH DOMAIN
CYSTEINE-POOR DOMAIN
UNIQUE DOMAINS

FIGURE 16

Pa

```
MSSCPVWRAMRSPSPPAWTTTGHCWPSRHLLP 40
GAAPRHGGHSRVPPLLQSGLASTHPLLNLTRSSRLLAGRV 80
SVEYWTREGLAMQRAARPHCLYAGHLQGQASSSHVAISTC 120
GGLHGLIVADEEEYLIEPLHGGPKGSRSPEESGPHVVYKR 160
SSLPHPHLDTACGVRDEKPWKGRPWWLRTLKPPPARPLGN 200
ETEPGQPGLKRSVSRERYVVETLVVADKMMVAYHGRRDVEQ 240
YVLAIMNIVAKLFQDSSLGSIVNILVTRLILLTEDQPTLE 280
ITHHAGHSLDSFCKWQKSIVNHSGHGNAIPENGVANHDTA 320
VLITRYDICIYKNKPCGTLGLARWAECVSAREAAASMRTL 360
AATSVHHCHEIGHTFGMNHDGVGNSCGARGQDPAKLMAAH 400
ITMTINPFVWSSCNRDYITSFLDSGLGLCLNNRPPRQDFV 440
YPTVAPGQAYDAEEQCRFQHGVKSRQCKYGEVCSELWCLS 480
KSNFCITNSIPAAEGTLCQTHTIDKGWCYKRVCVPFGSRP 520
EGVDGAWGPWTPWGDCSRTCGGGVSSSSRHCDSPRPTIGG 560
KYCLGERRRHRSCNTDDCPPGSQDFREVQCSEFDSIPFRG 600
KFYAWKTYRGGGVKACSLTSLAEGFNFYTERAAAVVDGTP 640
CRPDTVDICVSGECKHVGCDRVLGSDLREDKCRVCGGDGS 680
ACETTEGVFSPASPGAGYEDVVWIPKGSVHIFIQDLNLSL 720
SHLALKGDQESLLLEGLPGTPQPHRLPLAGTTFQLRQGPD 760
QVQSLEALGPLNASLIVMVLARTELPALRYRFNAPIARDS 800
LPPYSWHYAPWTKCSAQCAGGSQVQAVECRNQLDSSAVAP 840
HYCSAHSKLPKRQPACNTEPCPPDWVVGNWSLCSRSCDAG 880
VRSRSVVCQRRVSAAEEKALDDSACPQPRPPVLEACHGPT 920
CPPEWAALDWSECTPSCGPGLRHRVVLCKSADHRATLPPA 960
HCSPAAKPPATMRCNLRRCPPARWVAGEWGECSAQCGVGQ 1000
RQRSVRCTSHTGQASHECTEALRPPTTQQCEAKCDSPTPG 1040
DGPEECHDVNKVAYCPLVLKFQPCSRAYFRQMCCKTCQGH 1080
Created: Thursday, October 01, 1998 11:05 PM
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```
          10        20        30        40
          |         |         |         |
tcacgcacgccttccggtctcaagATGAGTTCCTGTCCAG 40
TCTGGAGAGTTATGAGATCGCCTTCCCCACCCGCGTGGAC 80
CACAACGGGGCACTGCTGGCCTTCTCGCCACCTCCTCCCC 120
GGAGCAGCGCCGCGGCACGGGGGCCACAGCCGAGTCCCGC 160
CTCTTCTACAAAGTGGCCTCGCCAGCACCCACTTCCTGCT 200
```

FIGURE 16 (continued)

Pa

```
        210         220         230         240
GAACCTGACCCGCAGCTCCCGTCTACTGGCAGGGCGCGTC 240
TCCGTGGAGTACTGGACACGGGAGGGCCTGGCCTGGCAGA 280
GGGCGGCCCCGGCCCCACTGCCTCTACGCTGGTCACCTGCA 320
GGGCCAGGCCAGCAGCTCCCATGTGGCCATCAGCACCTGT 360
GGAGGCCTGCACGGCCTGATCGTGGCAGACGAGGAAGAGT 400
        410         420         430         440
ACCTGATTGAGCCCCTGCACGGTGGGCCCAAGGGTTCTCG 440
GAGCCCGGAGGAAAGTGGACCACATGTGGTGTACAAGCGT 480
TCCTCTCTGCGTCACCCCCACCTGGACACAGCCTGTGGAG 520
TGAGAGATGAGAAACCGTGGAAAGGGCGGCCATGGTGGCT 560
GCGGACCTTGAAGCCACCGCCTGCCAGACCCCTGGGGAAT 600
        610         620         630         640
GAAACAGAGCGTGGCCAGCCAGGCCTGAAGCGATCGGTCA 640
GCCGAGAGCGCTACGTGGAGACCCTGGTGGTGGCTGACAA 680
GATGATGGTGGCCTATCACGGGCGCCGGGATGTGGAGCAG 720
TATGTCCTGGCCATCATGAACATTGTTGCCAAACTTTTCC 760
AGGACTCGAGTCTGGGAAGCACCGTTAACATCCTCGTAAC 800
        810         820         830         840
TCGCCTCATCCTGCTCACGGAGGACCAGCCCACTCTGGAG 840
ATCACCCACCATGCCGGGAAGTCCCTAGACAGCTTCTGTA 880
AGTGGCAGAAATCCATCGTGAACCACAGCGGCCATGGCAA 920
TGCCATTCCAGAGAACGGTGTGGCTAACCATGACACAGCA 960
GTGCTCATCACACGCTATGACATCTGCATCTACAAGAACA 1000
        1010        1020        1030        1040
AACCCTGCGGCACACTAGGCCTGGCCCGGTGGGCGGAATG 1040
TGTGACCGCGAGAGAAGCTGCAGCGTCAATGAGGACATTG 1080
GCTGCCACAAGCGTTCACCATTGCCACGAGATCGGGCACA 1120
CATTCGGCATGAACCATGACGGCGTGGGAAACAGCTGTGG 1160
```

FIGURE 16 (continued)

Pa

```
        1210        1220        1230        1240
ATTACCATGAAGACCAACCCATTCGTGTGGTCATCCTGCA 1240
ACCGTGACTACATCACCAGCTTTCTAGACTCGGGCCTGGG 1280
GCTCTGCCTGAACAACCGGCCCCCCAGACAGGACTTTGTG 1320
TACCCGACAGTGGCACCGGGCCAAGCCTACGATGCAGATG 1360
AGCAATGCCGCTTTCAGCATGGAGTCAAATCGCGTCAGTG 1400
        1410        1420        1430        1440
TAAATACGGGGAGGTCTGCAGCGAGCTGTGGTGTCTGAGC 1440
AAGAGCAACCGGTGCATCACCAACAGCATCCCGGCCGCCG 1480
AGGGCACGCTGTGCCAGACGCACACCATCGACAAGGGGTG 1520
GTGCTACAAACGGGTCTGTGTCCCCTTTGGGTCGCGCCCA 1560
GAGGGTGTGGACGGAGCCTGGGGGCCGTGGACTCCATGGG 1600
        1610        1620        1630        1640
GCGACTGCAGCCGGACCTGTGGCGGCGGCGTGTCCTCTTC 1640
TAGTCGTCACTGCGACAGCCCCAGGCCAACCATCGGGGGC 1680
AAGTACTGTCTGGGTGAGAGAAGGCGGCACCGCTCCTGCA 1720
ACACGGATGACTGTCCCCCTGGCTCCCAGGACTTCAGAGA 1760
AGTGCAGTGTTCTGAATTTGACAGCATCCCTTTCCGTGGG 1800
        1810        1820        1830        1840
AAATTCTACAAGTGGAAAACGTACCGGGGAGGGGGCGTGA 1840
AGGCCTGCTCGCTCACGAGCCTAGCGGAAGGCTTCAACTT 1880
CTACACGGAGAGGGCGGCAGCCGTGGTGGACGGGACACCC 1920
TGCCGTCCAGACACGGTGGACATTTGCGTCAGTGGCGAAT 1960
GCAAGCACGTGGGCTGCGACCGAGTCCTGGGCTCCGACCT 2000
        2010        2020        2030        2040
GCGGAGGACAAGTGCCGAGTGTGTGGCGGTGACGGCAGT 2040
GCTTGCGAGACCATCGAGGGCGTCTTCAGCCCAGCCTCAC 2080
CTGGGGCCGGTACGAGGATGTCGTCTGGATTCCCAAAGG 2120
CTCCGTCCACATCTTCATCCAGGATCTGAACCTCTCTCTC 2160
```

FIGURE 16 (continued)

Pa

```
        2210        2220        2230        2240
TGGAGGGGCTGCCTGGGACCCCCCAGCCCCACCGTCTGCC 2240
TCTAGCTGGGACCACCTTTCAACTGCGACAGGGGCCAGAC 2280
CAGGTCCAGAGCCTCGAAGCCCTGGGACCGATTAATGCAT 2320
CTCTCATCGTCATGGTGCTGGCCCGGACCGAGCTGCCTGC 2360
CCTCCGCTACCGCTTCAATGCCCCCATCGCCCGTGACTCG 2400
        2410        2420        2430        2440
CTGCCCCCCTACTCCTGGCACTATGCGCCCTGGACCAAGT 2440
GCTCGGCCCAGTGTGCAGGCGGTAGCCAGGTGCAGGCGGT 2480
GGAGTGCCGCAACCAGCTGGACAGCTCCGCGGTCGCCCCC 2520
CACTACTGCAGTGCCCACAGCAAGCTGCCCAAAAGGCAGC 2560
GCGCCTGCAACACGGAGCCTTGCCCTCCAGACTGGGTTGT 2600
        2610        2620        2630        2640
AGGGAACTGGTCGCTCTGCAGCCGCAGCTGCGATGCAGGC 2640
GTGCGCAGTCCGCTCGGTCGTGTGCCAGCGCCGCGTCTCTG 2680
CCGCGGAGGAGAAGGCGCTGGACGACAGCGCATGCCCGCA 2720
GCCGCGCCCACCTGTACTGGAGGCCTGCCACGGCCCCACT 2760
TGCCCTCCGGAGTGGGCGGCCCTCGACTGGTCTGAGTGCA 2800
        2810        2820        2830        2840
CCCCCAGCTGCGGGCCGGGCCTCCGCCACCGCGTGGTCCT 2840
TTGCAAGAGCGCAGACCACCGCGCCACGCTGCCCCGGCG 2880
CACTGCTCACCCGCCGCCAAGCCACCGGCCACCATGCGCT 2920
GCAACTTGCGCCGCTGCCCCCCGGCCCGCTGGGTGGCTGG 2960
CGAGTGGGGTGAGTGCTCTGCACAGTGCGGCGTCGGGCAG 3000
        3010        3020        3030        3040
CGGCAGCGCTCGGTGCGCTGCACCAGCCACACGGGCCAGG 3040
CGTCGCACGAGTGCACGGAGGCCCTGCGGCCGCCCACCAC 3080
GCAGCAGTGTGAGGCCAAGTGCGACAGCCCAACCCCCGGG 3120
GACGGCCCTGAAGAGTGCAAGGATGTGAACAAGGTCGCCT 3160
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FIGURE 16 (continued)

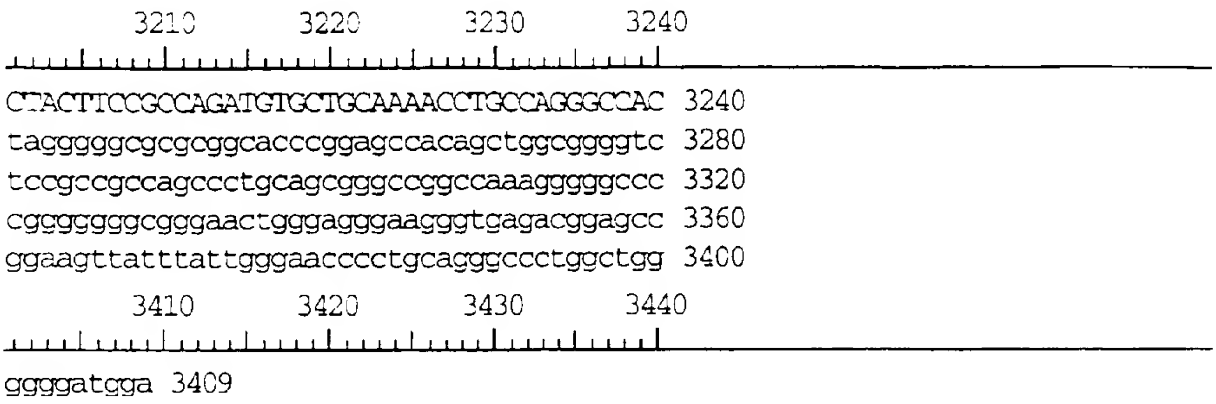

FIGURE 17

Molecular Weight 216301.30 Daltons
1934 Amino Acids
234 Strongly Basic(+) Amino Acids (K,R)
216 Strongly Acidic(-) Amino Acids (D,E)
477 Hydrophobic Amino Acids (A,I,L,F,W,V)
657 Polar Amino Acids (N,C,Q,S,T,Y)

7.734 Isolectric Point
24.102 Charge at PH 7.0

MQFVSWAILLVTLLVRDLAEMGSPDAAAAVRKDRLHPRQVKLLETLSEYEIVSPIRVNALG 60
EPFPINVHFKRTRRSINSATDPWPAFASSSSSSTSPQAHYRLSAFGQQFLFNLTANAGFI 120
APLFTVTLLGTPGVNQTKFYSEEEAELKHCFYKGYVNINSEHTAVISLCSGMLGTFRSHD 180
GGYFIEPLQSMDEQEDEEEQNKPHIIYRRSAPQREPSTGRHACDTSEHKNRHSKDKKTR 240
ARKWGERINLAGDVAALNSGLATEAFSAYGNKTDNIREKRTHRRTKRFLSYPRFVEVLVV 300
ADNRMVSYHGENLQHYILTLMSIVASIYKDPSIGNLINIVIVNLIVIHNEQDGPSISFNA 360
QTTLKNFCQWQHSNSPGGIHHDTAVLLTRQDICRAHDKCDITLGLAELGTICDPYRSCSIS 420
EDSGLSTAFTIAHELGHVFNMPHDDNNKCKEEGVKSPQHVMAPTLNFYTNPWMWSKCSRK 480
YITEFLDTGYGECLLNEPESRPYPLPVQLPGILYNVNKQCELIFGPGSQVCPYMMQCRRL 540
WCNVVNGVHKGCRTQHTPWADGTECEPGKHCKYGFCVPKEMDVPVTDGSWGSWSPFGTCS 600
RTCGGGIKTAIRECNRPEPKNGGKYCVGRRMKFKSCNTEPCLKQKRDFRDEQCAHFDGKH 660
FNTNGLLPNVFWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGQDTNDICVQ 720
GLCRQAGCDHVLNSKARRDKCGVCGGDNSSCKTVAGTFNTVHYGYNTVVRIPAGATNIDV 780
RQHSFSGEIDDDNYLALSSSKGEFLLNGNFVVTMAKREIRIGNAVVEYSGSETAVERINS 840
TDRIEQELLLQVLSVGKLYNPDVRYSFNIPIEDKPQQFYWNSHGPWQACSKPCQGERKRK 900
LVCTRESDQLTVSDQRCDRLPQPGHITEPCGTGCDLRWHVASRSECSAQCGLGYRTLDIY 960
CAKYSRLDGKTEKVDDGFCSSHPKPSNREKCSGECNTGGWRYSAWTECSKSCDGGTQRRR 1020
AICVNTRNDVLDDSKCTHQEKVTIQRCSEFPCPQWKSGDWSECLVTCGKGHKHRQVWCQF 1080
GEDFLNDRWCDPETKPTSMQTCQQPECASWQAGPWVQCSVTCGQGYQLRAVKCIIGTYMS 1140
VVDDNDCNAATRPTDTQDCELPSCHPPPAAPETRRSTYSAPRTQWRFGSWTPCSATCGKG 1200
TRMRYVSCFDENGSVADESACATLPRPVAKEECSVTPCGQWKALDWSSCSVTCGQGRATR 1260
QVMCVNYSDHVTDRSECDQDYIPETDQDCSMSPCPQRTPDSGLACHPFQNEDYRPRSASP 1320
SRTHVLGGNQWRTGPWGACSSTCAGGSQRRVVVCQDENGYTANDCVERIKPDEQPACESG 1380
PCPQWAYGNWGECTKLCGGGIRTRLVVCQRSNGERFPDLSCEILDKPPDREQCNTHACPH 1440
DAAWSTGPWSSCSVSCGRGHKQRNVYCMAKDGSHLESDYCKHLAKPHGHRKCRGGRCPKW 1500
KAGAWSQCSVSCGRGVQQRHVGCQIGTHKIAFETECNPYTRPESECECQGPRCPLYIWRA 1560
EEWQECTNTCGEGSRYRKVVCVDINKNEVHGARCDVSKRPVDRESCSLQPCEYVWITGEW 1620

[illegible]

FIGURE 17 (continued)

Pa

DCYSAAKCPQGRFSINLYGTGLSLTESARWLSQGNYAVSDIKKSPDGTRVVGKCGGYCGK 1920
CTPSSGTGLEVRVL 1934

10 20 30 40

tgggggcagcggagggaggggtgggaagcaccATGCAGTT 40
TGTATCCTGGGCCACACTGCTAACGCTCCTGGTGCGGGAC 80
CTGGCCGAGATGGGGAGCCCAGACGCCGCGGCGGCCGTGC 120
GCAAGGACAGGCTGCACCCGAGGCAAGTGAAATTATTAGA 160
GACCCTGAGCGAATACGAAATCGTGTCTCCCATCCGAGTG 200

210 220 230 240

AACGCTCTCGGAGAACCCTTTCCCACGAACGTCCACTTCA 240
AAAGAACGCGACGGAGCATTAACTCTGCCACTGACCCCTG 280
GCCTGCCTTCGCCTCCTCCTCTTCCTCCTCTACCTCCCCC 320
CAGGCGCATTACCGCCTCTCTGCCTTCGGCCAGCAGTTTC 360
TATTTAATCTCACCGCCAATGCCGGATTTATCGCTCCACT 400

410 420 430 440

GTTCACTGTCACCCTCCTCGGGACGCCCGGGGTGAATCAG 440
ACCAAGTTTTATTCCGAAGAGGAAGCGGAACTCAAGCACT 480
GTTTCTACAAAGGCTATGTCAATACCAACTCCGAGCACAC 520
GGCCGTCATCAGCCTCTGCTCAGGAATGCTGGGCACATTC 560
CGGTCTCATGATGGGGGTTATTTTATTGAACCACTACAGT 600

610 620 630 640

CTATGGATGAACAAGAAGATGAAGAGGAACAAAACAAACC 640
CCACATCATTTATAGGCGCAGCGCCCCCCAGAGAGAGCCC 680
TCAACAGGAAGGCATGCATGTGACACCTCAGAACACAAAA 720
ATAGGCACAGTAAAGACAAGAAGAAAACCAGAGCAAGAAA 760
ATGGGGAGAAAGGATTAACCTGGCTGGTGACGTAGCAGCA 800

810 820 830 840

[illegible]

[illegible]

FIGURE 17 (continued)

Pa

1010 1020 1030 1040

TGTAGCCTCTATCTATAAAGACCCAAGTATTGGAAATTTA 1040
ATTAATATTGTTATTGTGAACTTAATTGTGATTCATAATG 1080
AACAGGATGGGCCTTCCATATCTTTTAATGCTCAGACAAC 1120
ATTAAAAAACTTTTGCCAGTGGCAGCATTCGAACAGTCCA 1160
GGTGGAATCCATCATGATACTGCTGTTCTCTTAACAAGAC 1200

1210 1220 1230 1240

AGGATATCTGCAGAGCTCACGACAAATGTGATACCTTAGG 1240
CCTGGCTGAACTGGGAACCATTTGTGATCCCTATAGAAGC 1280
TGTTCTATTAGTGAAGATAGTGGATTGAGTACAGCTTTTA 1320
CGATCGCCCATGAGCTGGGCCATGTGTTTAACATGCCTCA 1360
TGATGACAACAACAAATGTAAAGAAGAAGGAGTTAAGAGT 1400

1410 1420 1430 1440

CCCCAGCATGTCATGGCTCCAACACTGAACTTCTACACCA 1440
ACCCCTGGATGTGGTCAAAGTGTAGTCGAAAATATATCAC 1480
TGAGTTTTTAGACACTGGTTATGGCGAGTGTTTGCTTAAC 1520
GAACCTGAATCCAGACCCTACCCTTTGCCTGTCCAACTGC 1560
CAGGCATCCTTTACAACGTGAATAAACAATGTGAATTGAT 1600

1610 1620 1630 1640

TTTTGGACCAGGTTCTCAGGTGTGCCCATATATGATGCAG 1640
TGCAGACGGCTCTGGTGCAATAACGTCAATGGAGTACACA 1680
AAGGCTGCCGGACTCAGCACACACCCTGGGCCGATGGGAC 1720
GGAGTGCGAGCCTGGAAAGCACTGCAAGTATGGATTTTGT 1760
GTTCCCAAAGAAATGGATGTCCCCGTGACAGATGGATCCT 1800

1810 1820 1830 1840

GGGGAAGTTGGAGTCCCTTTGGAACCTGCTCCAGAACATG 1840
TGGAGGGGGCATCAAAACAGCCATTCGAGAGTGCAACAGA 1880
CCAGAACCAAAAAATGGTGCAAAATACTGTGTAGGACGTA 1920
GAATGAAACTTAAGTCCTGCAACACGGAGCCATGTCTCAA 1960

FIGURE 17 (continued)

2010 2020 2030 2040

GACGGGAAGCATTTTAACATCAACGGTCTGCTTCCCAATG 2040
TGCGCTGGGTCCCTAAATACAGTGGAATTCTGATGAAGGA 2080
CCGGTGCAAGTTGTTCTGCAGAGTGGCAGGGAACACAGCC 2120
TACTATCAGCTTCGAGACAGAGTGATAGATGGAACTCCTT 2160
GTGGCCAGGACACAAATGATATCTGTGTCCAGGGCCTTTG 2200

2210 2220 2230 2240

CCGGCAAGCTGGATGCGATCATGTTTTAAACTCAAAAGCC 2240
CGGAGAGATAAATGCGGGGTTTGTGGTGGCGATAATTCTT 2280
CATGCAAAACAGTGGCAGGAACATTTAATACAGTACATTA 2320
TGGTTACAATACTGTGGTCCGAATTCCAGCTGGTGCTACC 2360
AATATTGATGTGCGGCAGCACAGTTTCTCAGGGGAAACAG 2400

2410 2420 2430 2440

ACGATGACAACTACTTAGCTTTATCAAGCAGTAAAGGTGA 2440
ATTCTTGCTAAATGGAAACTTTGTTGTCACAATGGCCAAA 2480
AGGGAAATTCGCATTGGGAATGCTGTGGTAGAGTACAGTG 2520
GGTCCGAGACTGCCGTAGAAAGAATTAACTCAACAGATCG 2560
CATTGAGCAAGAACTTTTGCTTCAGGTTTTGTCGGTGGGA 2600

2610 2620 2630 2640

AAGTTGTACAACCCCGATGTACGCTATTCTTTCAATATTC 2640
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2810 2820 2830 2840

TGGACACATTACTGAACCCTGTGGTACAGGCTGTGACCTG 2840
AGGTGGCATGTTGCCAGCAGGAGTGAATGTAGTGCCCAGT 2880
GTGGCTTGGGTTACCGCACATTGGACATCTACTGTGCCAA 2920
ATATAGCAGGCTGGATGGGAAGACTGAGAAGGTTGATGAT 2960

FIGURE 17 (continued)

Pa

```
        3010        3020        3030        3040
AATGCTCAGGGGAATGTAACACGGGTGGCTGGCGCTATTC 3040
TGCCTGGACTGAATGTTCAAAAAGCTGTGACGGTGGGACC 3080
CAGAGGAGAAGGGCTATTTGTGTCAATACCCGAAATGATG 3120
TACTGGATGACAGCAAATGCACACATCAAGAGAAAGTTAC 3160
CATTCAGAGGTGCAGTGAGTTCCCTTGTCCACAGTGGAAA 3200
        3210        3220        3230        3240
TCTGGAGACTGGTCAGAGTGCTTGGTCACCTGTGGAAAAG 3240
GGCATAAGCACCGCCAGGTCTGGTGTCAGTTTGGTGAAGA 3280
TCGATTAAATGATAGAATGTGTGACCCTGAGACCAAGCCA 3320
ACATCTATGCAGACTTGTCAGCAGCCGGAATGTGCATCCT 3360
GGCAGGCGGGTCCCTGGGTACAGTGCAGTGTCACTTGTGG 3400
        3410        3420        3430        3440
ACAGGGATACCAGCTAAGAGCAGTGAAATGCATCATTGGG 3440
ACTTATATGTCAGTGGTAGATGACAATGACTGTAATGCAG 3480
CAACTAGACCAACTGATACCCAGGACTGTGAATTACCATC 3520
ATGTCATCCTCCCCCAGCTGCCCCCGGAAACGAGGAGAAGC 3560
ACATACAGTGCACCAAGAACCCAGTGGCGATTTGGGTCTT 3600
        3610        3620        3630        3640
GGACCCCATGCTCAGCCACTTGTGGGAAAGGTACCCGGAT 3640
GAGATACGTCAGCTGCCGAGATGAGAATGGCTCTGTGGCT 3680
GACGAGAGTGCCTGTGCTACCCTGCCTAGACCAGTGGCAA 3720
AGGAAGAATGTTCTGTGACACCCTGTGGGCAATGGAAGGC 3760
CTTGGACTGGAGCTCTTGCTCTGTGACCTGTGGGCAAGGT 3800
        3810        3820        3830        3840
AGGGCAACCCGGCAAGTGATGTGTGTCAACTACAGTGACC 3840
ACGTGATCGATCGGAGTGAGTGTGACCAGGATTATATCGC 3880
AGAAACTGACCAGGACTGTTCCATGTCACCATGCCCTCAA 3920
AGGACCCCAGACAGTGGCTTAGCTCAGCACCCTTCCAAA 3960
```

FIGURE 17 (continued)

```
        4010        4020        4030        4040
CCATGTGCTCGGTGGAAACCAGTGGAGAACTGGCCCCTGG 4040
GGAGCATGTTCCAGTACCTGTGCTGGCGGATCCCAGCGGC 4080
GTGTTGTTGTATGTCAGGATGAAAATGGATACACCGCAAA 4120
CGACTGTGTGGAGAGAATAAAACCTGATGAGCAAAGAGCC 4160
TGTGAATCCGGCCCTTGTCCTCAGTGGGCTTATGGCAACT 4200
        4210        4220        4230        4240
GGGGAGAGTGCACTAAGCTGTGTGGTGGAGGCATAAGAAC 4240
AAGACTGGTGGTCTGTCAGCGGTCCAACGGTGAACGGTTT 4280
CCAGATTTGAGCTGTGAAATTCTTGATAAACCTCCCGATC 4320
GTGAGCAGTGTAACACACATGCTTGTCCACACGACGCTGC 4360
ATGGAGTACTGGCCCTTGGAGCTCGTGTTCTGTCTCTTGT 4400
        4410        4420        4430        4440
GGTCGAGGGCATAAACAACGAAATGTTTACTGCATGGCAA 4440
AAGATGGAAGCCATTTAGAAAGTGATTACTGTAAGCACCT 4480
GGCTAAGCCACATGGGCACAGAAAGTGCCGAGGAGGAAGA 4520
TGCCCCAAATGGAAAGCTGGCGCTTGGAGTCAGTGCTCTG 4560
TGTCCTGTGGCCGAGGCGTACAGCAGAGGCATGTGGGCTG 4600
        4610        4620        4630        4640
TCAGATCGGAACACACAAAATAGCCAGAGAGACCGAGTGC 4640
AACCCATACACCAGACCGGAGTCGGAATGCGAATGCCAAG 4680
GCCCACGGTGTCCCCTTCACACTTGGAGGGCAGAGGAATG 4720
GCAAGAATGCACCAAGACCTGCGGCGAAGGCTCCAGGTAC 4760
CGCAAGGTGGTGTGTGTGGATGACAACAAAAACGAGGTGC 4800
        4810        4820        4830        4840
ATGGGGCACGCTGTGACGTGAGCAAGCGGCCGGTGGACCG 4840
TGAAAGCTGTAGTTTGCAACCCTGCGAGTATGTCTGGATC 4880
ACAGGAGAATGGTCAGAGTGCTCAGTGACCTGTGGAAAAG 4920
GCCACAAACAAAGGCTTGTCTCGTGCAGCGAGATTTACAC 4960
```

FIGURE 17 (continued)

```
        5010        5020        5030        5040
AACTGCCCAGGCACGCAGCCCCCCAGTGTTCACCCCTGTT 5040
ACCTGAGGGAGTGCCCTGTCTCGGCCACCTGGAGAGTTGG 5080
CAACTGGGGGAGCTGCTCAGTGTCTTGTGGTGTTGGAGTG 5120
ATGCAGAGATCTGTGCAATGTTTAACCAATGAGGACCAAC 5160
CCAGCCACTTATGCCACACTGATCTGAAGCCAGAAGAACG 5200
        5210        5220        5230        5240
AAAAACCTGCCGTAATGTCTATAACTGTGAGTTACCCCAG 5240
AATTGCAAGGAGGTAAAAAGACTTAAAGGTGCCAGTGAAG 5280
ATGGTGAATATTTCCTGATGATTAGAGGAAAGCTTCTGAA 5320
GATATTCTGTGCGGGGATGCACTCTGACCACCCCAAAGAG 5360
TACGTGACACTGGTGCATGGAGACTCTGAGAATTTCTCCG 5400
        5410        5420        5430        5440
AGGTTTATGGGCACAGGTTACACAACCCAACAGAATGTCC 5440
CTATAACGGGAGCCGGTGCGATGACTGCCAATGTCGGAAG 5480
GATTACACGGCCGCTGGGTTTTCCAGTTTTCAGAAAATCA 5520
GAATAGACCTGACCAGCATGCAGATAATCACCACTGACTT 5560
ACAGTTTGCAAGGACAAGCGAAGGACATCCCGTCCCTTTT 5600
        5610        5620        5630        5640
GCCACAGCCGGGGATTGCTACAGCGCTGCCAAGTGCCCAC 5640
AGGGTCGTTTTAGCATCAACCTTTATGGAACCGGCTTGTC 5680
TTTAACTGAATCTGCCAGATGGATATCACAAGGGAATTAT 5720
GCTGTCTCTGACATCAAGAAGTCCGCCGGATGGTACCCGAG 5760
TCGTAGGGAAATGCGGTGGTTACTGTGGAAAATGCACTCC 5800
        5810        5820        5830        5840
ATCCTCTGGTACTGGCTGGAGGTGCGAGTTTTAtagcta 5840
aggtgctttgaagaggaagccattatggatggatgaagga 5880
tagtaatgcaatacctccaccttaatttgggtgcatgtgt 5920
atgtgtgtgtgtgtttgtgtgtgacttgtatgcttgtgtg 5960
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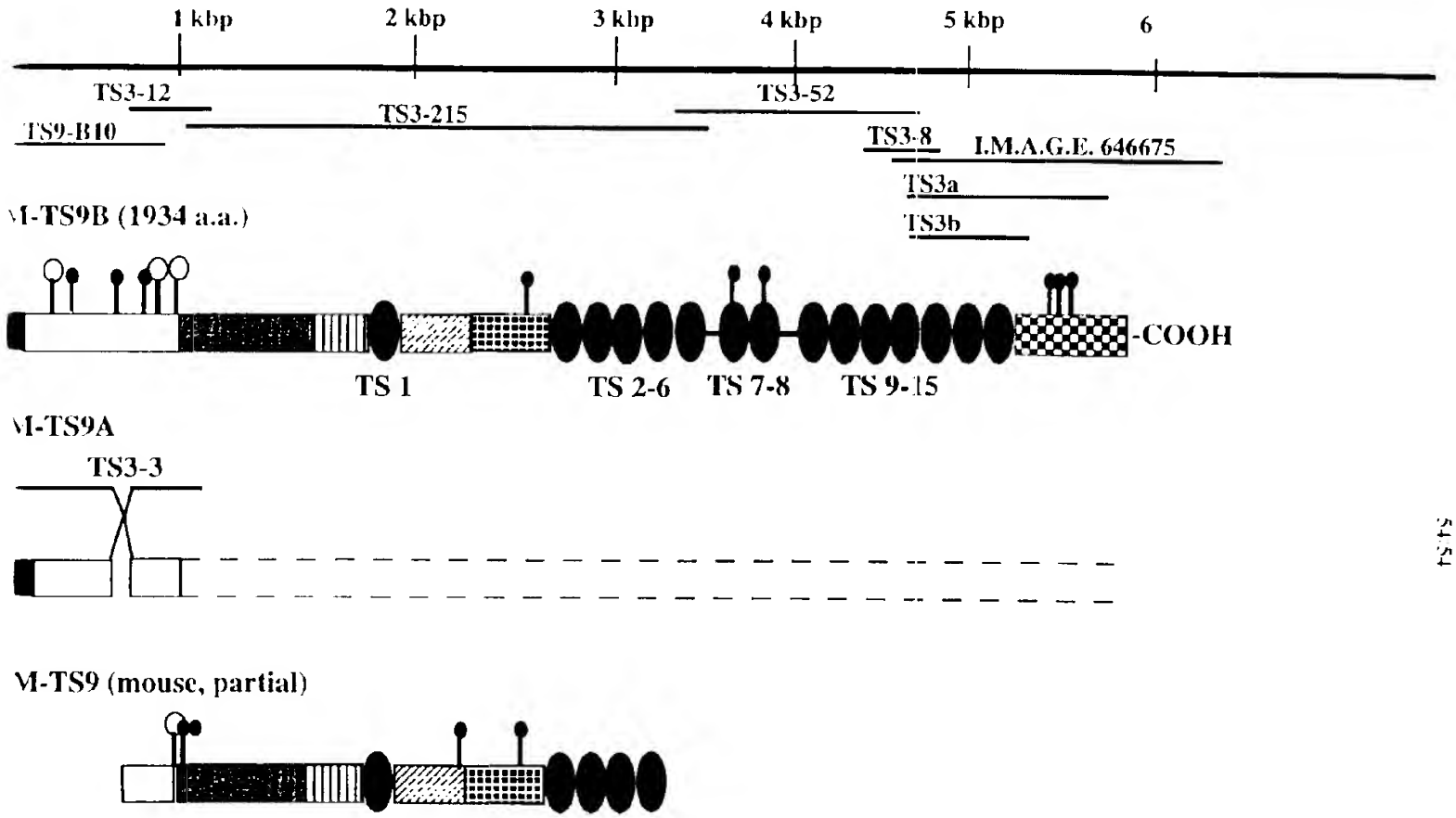
FIG



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Leu Leu Leu Leu Ser Ala Ser Cys Leu Ser Leu Ala Ala Asp Ser Pro
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Ala Ala Ala Pro Ala Gln Asp Lys Thr Arg Gln Pro Gln Ala Ala Ala
30 35 40

gcg gcc gcc gag ccg gac cag ccg cag ggg gag gaa aca cgg gag cga 194
Ala Ala Ala Glu Pro Asp Gln Pro Gln Gly Glu Glu Thr Arg Glu Arg
45 50 55

ggc cat tta caa ccc ttg gcc ggg cag cgc agg agc ggc ggg ctg gtc 242
Gly His Leu Gln Pro Leu Ala Gly Gln Arg Arg Ser Gly Gly Leu Val
60 65 70 75

cat aat ata gac caa ctc tac tct ggc ggt ggc aaa gtg ggc tac ctt 290
His Asn Ile Asp Gln Leu Tyr Ser Gly Gly Gly Lys Val Gly Tyr Leu
80 85 90

gtc tac gcg ggc ggc cgg agg ttc ctg ctg gac ctg gag aga gat gac 338
Val Tyr Ala Gly Gly Arg Arg Phe Leu Leu Asp Leu Glu Arg Asp Asp
95 100 105

aca gtg ggt gct gct ggt agc atc gtt act gta gga ggg ggg ctg agc 386
Thr Val Gly Ala Ala Gly Ser Ile Val Thr Ala Gly Gly Gly Leu Ser
110 115 120

[illegible]
Gly Ser Ile Arg Asn [illegible] Ala Val Ile Asp [illegible] [illegible] Gly [illegible]
140 145 150 155

```
   ggc ttc ttt gca gtc aag cat gcg cgc tac act cta aag cca ctc ctg   530
   Gly Phe Phe Ala Val Lys His Ala Arg Tyr Thr Leu Lys Pro Leu Leu
                   160                 165                 170
5
   cgt ggg tcc tgg gca gag tat gaa cga att tat ggg gat gga tct tcc   578
   Arg Gly Ser Trp Ala Glu Tyr Glu Arg Ile Tyr Gly Asp Gly Ser Ser
               175                 180                 185

10 cgc atc ctg cat gtc tac aac cgc gag ggc ttt agc ttc gag gcc ctg   626
   Arg Ile Leu His Val Tyr Asn Arg Glu Gly Phe Ser Phe Glu Ala Leu
           190                 195                 200

   ccg cca cgc gcc agt tgc gag act cct gca tcc cca tct ggg ccc caa   674
15 Pro Pro Arg Ala Ser Cys Glu Thr Pro Ala Ser Pro Ser Gly Pro Gln
       205                 210                 215

   gag agc ccc tcg gtg cac agt aga tct agg aga cgc tca gcg ctg gcc   722
   Glu Ser Pro Ser Val His Ser Arg Ser Arg Arg Arg Ser Ala Leu Ala
20 220                 225                 230                 235

   ccg cag ctg ctg gac cac tca gct ttc tcg cca tct ggg aac gcg gga   770
   Pro Gln Leu Leu Asp His Ser Ala Phe Ser Pro Ser Gly Asn Ala Gly
                   240                 245                 250
25
   cct cag act tgg tgg agg cgt agg cgc cgt tcc atc tcc agg gcc cgc   818
   Pro Gln Thr Trp Trp Arg Arg Arg Arg Arg Ser Ile Ser Arg Ala Arg
               255                 260                 265

30 cag gtg gag ctc ctc ttg gtg gct gac tcg tcc atg gcc agg atg tat   866
   Gln Val Glu Leu Leu Leu Val Ala Asp Ser Ser Met Ala Arg Met Tyr
           270                 275                 280

   ggg cgg ggc ctg cag cat tac ctg ctg acc atg gcc tcc atc gcc aac   914
35 Gly Arg Gly Leu Gln His Tyr Leu Leu Thr Met Ala Ser Ile Ala Asn
       285                 290                 295

   agg ctg tac agt cat gca agc att gag aac cac atc cgc ctg gcg gtg   962
   Arg Leu Tyr Ser His Ala Ser Ile Glu Asn His Ile Arg Leu Ala Val
40 300                 305                 310                 315

   gtg aag gtg gtg gtg ctg acg gac aag gac acg agt ctg gag gtg agc  1010
   Val Lys Val Val Val Leu Thr Asp Lys Asp Thr Ser Leu Glu Val Ser
                   320                 325                 330
45
   aag aat gcg gcc acg acc ctc aag aac ttt tgc aaa tgg cag cac cag  1058
   Lys Asn Ala Ala Thr Thr Leu Lys Asn Phe Cys Lys Trp Gln His Gln
               335                 340                 345

50 cat aac cag cta ggg gat gat cac gaa gag cac tat gat gca gcc atc  1106
   His Asn Gln Leu Gly Asp Asp His Glu Glu His Tyr Asp Ala Ala Ile
           350                 355                 360

   ctg ttc acc cga gag gat tta tgt ggg cat cat tca tgt gac acc ctg  1154
55 Leu Phe Thr Arg Glu Asp Leu Cys Gly His His Ser Cys Asp Thr Leu
       365                 370                 375

   aaa aac agg aac ttt ggg agc atc gcc ctc ttt tct gcc atg cgc agc  1202
```

```
   att ggg cat cta ctt gac ctt tct cat gac gtt tcc aaa tta cgt gaa
```

```
   Ile Gly His Leu Leu Gly Leu Ser His Asp Asp Ser Lys Phe Cys Glu
                415                 420                 425

   gag aac ttc ggt act aca gaa gac aag cgt tta atg tct tca atc ctt   1346
 5 Glu Asn Phe Gly Thr Thr Glu Asp Lys Arg Leu Met Ser Ser Ile Leu
            430                 435                 440

   acc agc atc gat gca tcc aag ccc tgg tcc aaa tgc acg tca gcc acc   1394
   Thr Ser Ile Asp Ala Ser Lys Pro Trp Ser Lys Cys Thr Ser Ala Thr
10      445                 450                 455

   atc aca gaa ttc ctg gat gat ggt cat ggt aat tgt ttg cta gac cta   1442
   Ile Thr Glu Phe Leu Asp Asp Gly His Gly Asn Cys Leu Leu Asp Leu
   460                 465                 470                 475
15
   cca cgg aag cag att ttg ggt ccc gag gaa ctc cca gga cag acc tac   1490
   Pro Arg Lys Gln Ile Leu Gly Pro Glu Glu Leu Pro Gly Gln Thr Tyr
                480                 485                 490

20 gat gcc acc cag cag tgc aac ttg aca ttt ggg cct gag tac tcg gtg   1538
   Asp Ala Thr Gln Gln Cys Asn Leu Thr Phe Gly Pro Glu Tyr Ser Val
                495                 500                 505

   tgc cct ggc atg gat gtc tgt gcg cgg ctg tgg tgt gct gtg gtg cgc   1586
25 Cys Pro Gly Met Asp Val Cys Ala Arg Leu Trp Cys Ala Val Val Arg
            510                 515                 520

   caa ggc caa atg gtg tgt ctg acc aag aag ctg ccg gct gtg gag ggc   1634
   Gln Gly Gln Met Val Cys Leu Thr Lys Lys Leu Pro Ala Val Glu Gly
30      525                 530                 535

   act ccc tgt ggg aag gga aga gtc tgc ctt caa ggc aaa tgt gtg gac   1682
   Thr Pro Cys Gly Lys Gly Arg Val Cys Leu Gln Gly Lys Cys Val Asp
   540                 545                 550                 555
35
   aaa act aag aaa aaa tat tac tcg aca tca agc cat gga aat tgg ggg   1730
   Lys Thr Lys Lys Lys Tyr Tyr Ser Thr Ser Ser His Gly Asn Trp Gly
                560                 565                 570

40 tcc tgg ggc ccc tgg ggt cag tgt tct cgc tca tgc ggg gga gga gtg   1778
   Ser Trp Gly Pro Trp Gly Gln Cys Ser Arg Ser Cys Gly Gly Gly Val
            575                 580                 585

   cag ttt gcc tac cgc cat tgt aat aac cct gca cct cga aac agt ggc   1826
45 Gln Phe Ala Tyr Arg His Cys Asn Asn Pro Ala Pro Arg Asn Ser Gly
        590                 595                 600

   agc tac tgt cac ggg aag agg gcc ata tac cgt tcc tgc agt gtt acc   1874
   Arg Tyr Cys His Gly Lys Arg Ala Ile Tyr Arg Ser Cys Ser Val Thr
50      605                 610                 615

   ccc tgc cca ccc aat ggt aaa tct ttt cgc cat gag cag tgt gaa gcc   1922
   Pro Cys Pro Pro Asn Gly Lys Ser Phe Arg His Glu Gln Cys Glu Ala
   620                 625                 630                 635
55
   aaa aat ggc tat cag tct gat gca aaa gga gtc aaa aca ttt gta gaa   1970
   Lys Asn Gly Tyr Gln Ser Asp Ala Lys Gly Val Lys Thr Phe Val Glu
                640                 645                 650

   ata [illegible]
   Ile [illegible]
```

```
   gtt acg gat ggg act gaa tgc agg ccg tac agc aac tct gtg tgt gtc   2114
   Val Thr Asp Gly Thr Glu Cys Arg Pro Tyr Ser Asn Ser Val Cys Val
       685                 690                 695
5
   cga gga cgg tgt gtg aga act gga tgt gac ggc att att ggc tca aag   2162
   Arg Gly Arg Cys Val Arg Thr Gly Cys Asp Gly Ile Ile Gly Ser Lys
   700                 705                 710                 715

10 cta caa tat gac aag tgt gga gtg tgc gga ggg gat aac tcc agt tgt   2210
   Leu Gln Tyr Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
                   720                 725                 730

   aca aag att atc gga acc ttc aat aaa aaa agc aag ggt tat act gac   2258
15 Thr Lys Ile Ile Gly Thr Phe Asn Lys Lys Ser Lys Gly Tyr Thr Asp
               735                 740                 745

   gtt gtg agg atc cct gaa gga gca acc cac ata aaa gtc cga cag ttc   2306
   Val Val Arg Ile Pro Glu Gly Ala Thr His Ile Lys Val Arg Gln Phe
20         750                 755                 760

   aaa gcc aaa gac cag act aga ttc cct gcc tac tta gcc ctg aag aag   2354
   Lys Ala Lys Asp Gln Thr Arg Phe Pro Ala Tyr Leu Ala Leu Lys Lys
       765                 770                 775
25
   aaa act ggc gag tac ctt atc aat ggc aag tac atg att tcc act tca   2402
   Lys Thr Gly Glu Tyr Leu Ile Asn Gly Lys Tyr Met Ile Ser Thr Ser
   780                 785                 790                 795

30 gag acc atc atc gac atc aat ggt acc gtc atg aac tac agt gga tgg   2450
   Glu Thr Ile Ile Asp Ile Asn Gly Thr Val Met Asn Tyr Ser Gly Trp
                   800                 805                 810

   agc cac aga gat gat ttt tta cat ggg atg ggc tat tca gcc aca aaa   2498
35 Ser His Arg Asp Asp Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys
               815                 820                 825

   gaa atc ctg atc gtg cag atc ctt gcc aca gac cca act aaa gcg cta   2546
   Glu Ile Leu Ile Val Gln Ile Leu Ala Thr Asp Pro Thr Lys Ala Leu
40         830                 835                 840

   ggc gtc cgt tac agc ttt ttt gtt ccc aag aag acc act caa aaa gta   2594
   Gly Val Arg Tyr Ser Phe Phe Val Pro Lys Lys Thr Thr Gln Lys Val
       845                 850                 855
45
   aac tct gtc atc agc cat ggc agt aac aag gtg gga cca cac tct aca   2642
   Asn Ser Val Ile Ser His Gly Ser Asn Lys Val Gly Pro His Ser Thr
   860                 865                 870                 875

50 cag ttg cag tgg gtg aca ggt cca tgg ctg gcc tgc tct agg acc tgt   2690
   Gln Leu Gln Trp Val Thr Gly Pro Trp Leu Ala Cys Ser Arg Thr Cys
                   880                 885                 890

   gac aca ggc tgg cac act agg acc gtg cag tgc cag gat gga aac agg   2738
55 Asp Thr Gly Trp His Thr Arg Thr Val Gln Cys Gln Asp Gly Asn Arg
               895                 900                 905

   aga tta ccc aga tta tgc ctt ccc tct cag agg cct tct gca ttt gac   2786
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             20                  25                  30
Gln Asp Lys Thr Arg Gln Pro Gln Ala Ala Ala Ala Ala Ala Glu Pro
         35                  40                  45
Asp Gln Pro Gln Gly Glu Glu Thr Arg Glu Arg Gly His Leu Gln Pro
     50                  55                  60
Leu Ala Gly Gln Arg Arg Ser Gly Gly Leu Val His Asn Ile Asp Gln
 65                  70                  75                  80
Leu Tyr Ser Gly Gly Gly Lys Val Gly Tyr Leu Val Tyr Ala Gly Gly
                 85                  90                  95
Arg Arg Phe Leu Leu Asp Leu Glu Arg Asp Asp Thr Val Gly Ala Ala
            100                 105                 110
Gly Ser Ile Val Thr Ala Gly Gly Gly Leu Ser Ala Ser Ser Gly His
        115                 120                 125
Arg Gly His Cys Phe Tyr Arg Gly Thr Val Asp Gly Ser Pro Arg Ser
    130                 135                 140
Leu Ala Val Phe Asp Leu Cys Gly Gly Leu Asp Gly Phe Phe Ala Val
145                 150                 155                 160
Lys His Ala Arg Tyr Thr Leu Lys Pro Leu Leu Arg Gly Ser Trp Ala
                165                 170                 175
Glu Tyr Glu Arg Ile Tyr Gly Asp Gly Ser Ser Arg Ile Leu His Val
            180                 185                 190
Tyr Asn Arg Glu Gly Phe Ser Phe Glu Ala Leu Pro Pro Arg Ala Ser
        195                 200                 205
Cys Glu Thr Pro Ala Ser Pro Ser Gly Pro Gln Glu Ser Pro Ser Val
    210                 215                 220
His Ser Arg Ser Arg Arg Arg Ser Ala Leu Ala Pro Gln Leu Leu Asp
225                 230                 235                 240
His Ser Ala Phe Ser Pro Ser Gly Asn Ala Gly Pro Gln Thr Trp Trp
                245                 250                 255
Arg Arg Arg Arg Arg Ser Ile Ser Arg Ala Arg Gln Val Glu Leu Leu
            260                 265                 270
Leu Val Ala Asp Ser Ser Met Ala Arg Met Tyr Gly Arg Gly Leu Gln
        275                 280                 285
His Tyr Leu Leu Thr Met Ala Ser Ile Ala Asn Arg Leu Tyr Ser His
    290                 295                 300
Ala Ser Ile Glu Asn His Ile Arg Leu Ala Val Val Lys Val Val Val
305                 310                 315                 320
Leu Thr Asp Lys Asp Thr Ser Leu Glu Val Ser Lys Asn Ala Ala Thr
                325                 330                 335
Thr Leu Lys Asn Phe Cys Lys Trp Gln His Gln His Asn Gln Leu Gly
            340                 345                 350
Asp Asp His Glu Glu His Tyr Asp Ala Ala Ile Leu Phe Thr Arg Glu
        355                 360                 365

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Leu Gly Pro Glu Glu Leu Pro Gly Gln Thr Tyr Asp Ala Thr Gln Gln
485 490 495
Cys Asn Leu Thr Phe Gly Pro Glu Tyr Ser Val Cys Pro Gly Met Asp
500 505 510
Val Cys Ala Arg Leu Trp Cys Ala Val Val Arg Gln Gly Gln Met Val
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Cys Leu Thr Lys Lys Leu Pro Ala Val Glu Gly Thr Pro Cys Gly Lys
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Gly Arg Val Cys Leu Gln Gly Lys Cys Val Asp Lys Thr Lys Lys Lys
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580 585 590
His Cys Asn Asn Pro Ala Pro Arg Asn Ser Gly Arg Tyr Cys Thr Gly
595 600 605
Lys Arg Ala Ile Tyr Arg Ser Cys Ser Val Thr Pro Cys Pro Pro Asn
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625 630 635 640
Ser Asp Ala Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro Lys Tyr
645 650 655
Ala Gly Val Leu Pro Ala Asp Val Cys Lys Leu Thr Cys Arg Ala Lys
660 665 670
Gly Thr Gly Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr
675 680 685
Glu Cys Arg Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Arg Cys Val
690 695 700
Arg Thr Gly Cys Asp Gly Ile Ile Gly Ser Lys Leu Gln Tyr Asp Lys
705 710 715 720
Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Ile Ile Gly
725 730 735
Thr Phe Asn Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro
740 745 750
Glu Gly Ala Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys Asp Gln
755 760 765
Thr Arg Phe Pro Ala Tyr Leu Ala Leu Lys Lys Lys Thr Gly Glu Tyr
770 775 780
Leu Ile Asn Gly Lys Tyr Met Ile Ser Thr Ser Glu Thr Ile Ile Asp
785 790 795 800
Ile Asn Gly Thr Val Met Asn Tyr Ser Gly Trp Ser His Arg Asp Asp
805 810 815
Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu Ile Val
820 825 830
Gln Ile Leu Ala Thr Asp Pro Thr Lys Ala Leu Gly Val Arg Tyr Ser
835 840 845
Phe Phe Val Pro Lys Lys Thr Thr Gln Lys Val Asn Ser Val Ile Ser
850 855 860
His Gly Ser Asn Lys Val Gly Pro His Ser Thr Gln Leu Gln Trp Val
865 870 875 880
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gagtgcagtt tgcctatcgt cactgtaata acgctgctcc cagaaacaac ggacgctact 420
gcacagggaa gagggccatc taccactcct gcagttctcat gccctgccca cccaatggta 480
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tcaaaacttt tgtggaatgg gttcccaaat atgcaggtgt cctgccagcg gatgtgtgca 600
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atggcactga atgtaggccg tacagtaatt ccgtctgcgt ctgggggaag tgtgtgagaa 720
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aagaccagac tagattcact gcctatttag cctgtaaaaa gaaaaacggt gagtacctta 960
tcaatggaaa gtacatgatc tccacttcag agactatcat tgacatcaat ggaacagtca 1020
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cgaaggaaat tctaatagtg cagattcttg caacagaccc cactaaacca ttagatgtcc 1140
gttatagctt ttttgttccc aagaagtcca ctccaaaagt aaactctgtc actagtcatg 1200
gcagcaataa agtgggatca cacacttcgc agccgcagtg ggtcacgggc ccatggctcg 1260
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1 5 10

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Ile Leu Ser Leu Ile Met Ala Ser Ser Glu Phe His Ser Asp His Arg
15 20 25

ttt act gtg gaa aat gat aaa tac ttc agg aga aga tgg agt atg gac 147

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    Phe Thr Val Lys Asn Asp Lys His Ser Arg Arg Arg Arg Ser Met Asp
         60                  65                  70

    cct att gat cca cag cag gca gta tct aag tta ttt ttt aaa ctt tca   291
 5  Pro Ile Asp Pro Gln Gln Ala Val Ser Lys Leu Phe Phe Lys Leu Ser
     75                  80                  85                  90

    gcc tat ggc aag cac ttt cat cta aac ttg act ctc aac aca gat ttt   339
    Ala Tyr Gly Lys His Phe His Leu Asn Leu Thr Leu Asn Thr Asp Phe
10                  95                 100                 105

    gtg tcc aaa cat ttt aca gta gaa tat tgg ggg aaa gat gga ccc cag   387
    Val Ser Lys His Phe Thr Val Glu Tyr Trp Gly Lys Asp Gly Pro Gln
                110                 115                 120
15
    tgg aaa cat gat ttt tta gac aac tgt cat tac aca gga tat ttg caa   435
    Trp Lys His Asp Phe Leu Asp Asn Cys His Tyr Thr Gly Tyr Leu Gln
            125                 130                 135

20  gat caa cgt agt aca act aaa gtg gct tta agc aac tgt gtt ggg ttg   483
    Asp Gln Arg Ser Thr Thr Lys Val Ala Leu Ser Asn Cys Val Gly Leu
        140                 145                 150

    cat ggt gtt att gct aca gaa gat gaa gag tat ttt atc gaa cct tta   531
25  His Gly Val Ile Ala Thr Glu Asp Glu Glu Tyr Phe Ile Glu Pro Leu
    155                 160                 165                 170

    aag aat acc aca gag gat tcc aag cat ttt agt tat gaa aat ggc cac   579
    Lys Asn Thr Thr Glu Asp Ser Lys His Phe Ser Tyr Glu Asn Gly His
30                  175                 180                 185

    cct cat gtt att tac aaa aag tct gcc ctt caa caa cga cat ctg tat   627
    Pro His Val Ile Tyr Lys Lys Ser Ala Leu Gln Gln Arg His Leu Tyr
                190                 195                 200
35
    gat cac tct cat tgt ggg gtt tcg gat ttc aca aga agt ggc aaa cct   675
    Asp His Ser His Cys Gly Val Ser Asp Phe Thr Arg Ser Gly Lys Pro
            205                 210                 215

40  tgg tgg ctg aat gac act cca ctg ttt ctt att cac tac caa att aac   723
    Trp Trp Leu Asn Asp Thr Pro Leu Phe Leu Ile His Tyr Gln Ile Asn
        220                 225                 230

    aac aca cat atc cac cac aga cag aag aga tca gtg agc att gaa cgg   771
45  Asn Thr His Ile His His Arg Gln Lys Arg Ser Val Ser Ile Glu Arg
    235                 240                 245                 250

    ttt gtg gag act ttg gta gtg gca gac aaa atg atg gtg ggc tac cat   819
    Phe Val Glu Thr Leu Val Val Ala Asp Lys Met Met Val Gly Tyr His
50                  255                 260                 265

    ggc cgc aaa gac att gaa cat tac att ttg agt gtg atg aat att gtt   867
    Gly Arg Lys Asp Ile Glu His Tyr Ile Leu Ser Val Met Asn Ile Val
                270                 275                 280
55
    gcc aaa ctt tac cgt gat tcc agc cta gga aac gtt gtg aat att ata   915
    Ala Lys Leu Tyr Arg Asp Ser Ser Leu Gly Asn Val Val Asn Ile Ile
            285                 290                 295

    [illegible]
    Asn His [illegible] Ala Arg Lys [illegible] Leu [illegible] [illegible] Tyr [illegible] [illegible] [illegible] Lys
    300                 305                 310                 315
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    tcc att ctc tcc cac caa agt gat gga aac acc att cca gaa aat ggg   1099
    Ser Ile Leu Ser His Gln Ser Asp Gly Asn Thr Ile Pro Glu Asn Gly
                    335                 340                 345

    att gcc cac cac gat aat gca gtt ctt att act aga tat gat atc tgc   1147
    Ile Ala His His Asp Asn Ala Val Leu Ile Thr Arg Tyr Asp Ile Cys
                350                 355                 360

    act tat aaa aat aag ccc tgt gga aca ctg ggc ttg gcc tct gtg gct   1195
    Thr Tyr Lys Asn Lys Pro Cys Gly Thr Leu Gly Leu Ala Ser Val Ala
            365                 370                 375

    gga atg tgt gag cct gaa agg agc tgc agc att aat gaa gac att ggc   1243
    Gly Met Cys Glu Pro Glu Arg Ser Cys Ser Ile Asn Glu Asp Ile Gly
        380                 385                 390

    ctg ggt tca gct ttt acc att gca cat gag att gtt cac aat ttt ggt   1291
    Leu Gly Ser Ala Phe Thr Ile Ala His Glu Ile Val His Asn Phe Gly
    395                 400                 405                 410

    atg aac cat gat gga att gga aat tct tgt gga cga aag gtc atg aag   1339
    Met Asn His Asp Gly Ile Gly Asn Ser Cys Gly Arg Lys Val Met Lys
                    415                 420                 425

    cag caa aat tat ggc agc tca cat tac tgc gaa tac caa tcc ttt ttc   1387
    Gln Gln Asn Tyr Gly Ser Ser His Tyr Cys Glu Tyr Gln Ser Phe Phe
                430                 435                 440

    ctg gtc tgc ttg cag tcg aga nta cat cac cag ctt ttt aga gaa gtg   1435
    Leu Val Cys Leu Gln Ser Arg Xaa His His Gln Leu Phe Arg Glu Val
            445                 450                 455

    tgt aga gag ctc tgg tgt ctc agc aaa agc aac cgc tgt gtc acc aac   1483
    Cys Arg Glu Leu Trp Cys Leu Ser Lys Ser Asn Arg Cys Val Thr Asn
        460                 465                 470

    agt att cca gca gct gag ggg aca ctg tgt caa act ggg aat att gaa   1531
    Ser Ile Pro Ala Ala Glu Gly Thr Leu Cys Gln Thr Gly Asn Ile Glu
    475                 480                 485                 490

    aaa ggg tgg tgt tat cag gga gat tgt gtt cct ttt ggc act tgg ccc   1579
    Lys Gly Trp Cys Tyr Gln Gly Asp Cys Val Pro Phe Gly Thr Trp Pro
                    495                 500                 505

    cag agc att gat ggg ggc tgg ggt cct tgg tca ctt tgg gga gag tgc   1627
    Gln Ser Ile Asp Gly Gly Trp Gly Pro Trp Ser Leu Trp Gly Glu Cys
                510                 515                 520

    agt agg acc tgt ggg gga ggc gtt tcc tca agc cta aga cac tgt gac   1675
    Ser Arg Thr Cys Gly Gly Gly Val Ser Ser Ser Leu Arg His Cys Asp
            525                 530                 535

    agt cca gca cct tcg gag gtg gaa aaa tat tgc ctt ggg gaa agg aaa   1723
    Ser Pro Ala Pro Ser Glu Val Glu Lys Tyr Cys Leu Gly Glu Arg Lys
        540                 545                 550

    [illegible]                                                      1771

    aag tat tct aat tgg aaa [illegible]                              1819
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   Lys Tyr Tyr Asn Trp Lys Pro Tyr Thr Gly Gly Gly Val Lys Pro Cys
                590                 595                 600

   gca tta aac tgc ttg gct gaa ggt tat aat ttc tac act gaa cgt gct  1875
 5 Ala Leu Asn Cys Leu Ala Glu Gly Tyr Asn Phe Tyr Thr Glu Arg Ala
          605                 610                 615

   cct gcg gtg atc gat ggg acc cag tgc aat gcg gat tca ctg gat atc  1923
   Pro Ala Val Ile Asp Gly Thr Gln Cys Asn Ala Asp Ser Leu Asp Ile
10      620                 625                 630

   tgc atc aat gga gaa tgc aag cac gta ggc tgt gat aat att ttg gga  1971
   Cys Ile Asn Gly Glu Cys Lys His Val Gly Cys Asp Asn Ile Leu Gly
   635                 640                 645                 650
15
   tct gat gct agg gaa gat aga tgt cga gtc tgt gga ggg ggc gga agc  2019
   Ser Asp Ala Arg Glu Asp Arg Cys Arg Val Cys Gly Gly Gly Gly Ser
                   655                 660                 665

20 aca tgt gat gcc att gaa ggg ttc ttc aat gat tca ctg ccc agg gga  2067
   Thr Cys Asp Ala Ile Glu Gly Phe Phe Asn Asp Ser Leu Pro Arg Gly
               670                 675                 680

   ggc tac atg gaa gtg gtg cag ata cca aga ggc tct gtt cac att gaa  2115
25 Gly Tyr Met Glu Val Val Gln Ile Pro Arg Gly Ser Val His Ile Glu
          685                 690                 695

   gtt aga gaa gtt gcc atg tca aag aac tat att gct tta aaa tct gaa  2163
   Val Arg Glu Val Ala Met Ser Lys Asn Tyr Ile Ala Leu Lys Ser Glu
30      700                 705                 710

   gga gat gat tac tat att aat ggt gcc tgg act att gac tgg cct agg  2211
   Gly Asp Asp Tyr Tyr Ile Asn Gly Ala Trp Thr Ile Asp Trp Pro Arg
   715                 720                 725                 730
35
   aaa ttt gat gtt gct ggg aca gct ttt cat tac aag aga cca act gat  2259
   Lys Phe Asp Val Ala Gly Thr Ala Phe His Tyr Lys Arg Pro Thr Asp
                   735                 740                 745

40 gaa cca gaa tcc ttg gaa gct cta ggt cct acc tca gaa aat ctc atc  2307
   Glu Pro Glu Ser Leu Glu Ala Leu Gly Pro Thr Ser Glu Asn Leu Ile
               750                 755                 760

   gtc atg gtt ctg ctt caa gaa cag aat ttg gga att agg tat aag ttc  2355
45 Val Met Val Leu Leu Gln Glu Gln Asn Leu Gly Ile Arg Tyr Lys Phe
          765                 770                 775

   aat gtt cct att act aga act ggc agt gga gat aat gaa gtt ggt ttt  2403
   Asn Val Pro Ile Thr Arg Thr Gly Ser Gly Asp Asn Glu Val Gly Phe
50      780                 785                 790

   aca tgg aat cat cag cct tgg tca gaa tgc tca gct act tgt gct gga  2451
   Thr Trp Asn His Gln Pro Trp Ser Glu Cys Ser Ala Thr Cys Ala Gly
   795                 800                 805                 810
55
   ggt aag atg cct act agg cag cct act cag agg gca aga tgg aga aca  2499
   Gly Lys Met Pro Thr Arg Gln Pro Thr Gln Arg Ala Arg Trp Arg Thr
                   815                 820                 825

   [illegible]
          845                 850                 855
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Leu
860

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tgaaggtggg ctgtttgcct ttcgtgaaca cattcttggt aaagaacatc aaaagtttta 2771

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gagaatgtac ggctgtg 2848

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35 40 45
Arg Val Asp Gln Asn Gly Ala Phe Leu Ser Phe Thr Val Lys Asn Asp
50 55 60
Lys His Ser Arg Arg Arg Arg Ser Met Asp Pro Ile Asp Pro Gln Gln
65 70 75 80
Ala Val Ser Lys Leu Phe Phe Lys Leu Ser Ala Tyr Gly Lys His Phe
85 90 95
His Leu Asn Leu Thr Leu Asn Thr Asp Phe Val Ser Lys His Phe Thr
100 105 110
Val Glu Tyr Trp Gly Lys Asp Gly Pro Gln Trp Lys His Asp Phe Leu
115 120 125
Asp Asn Cys His Tyr Thr Gly Tyr Leu Gln Asp Gln Arg Ser Thr Thr
130 135 140
Lys Val Ala Leu Ser Asn Cys Val Gly Leu His Gly Val Ile Ala Thr
145 150 155 160
Glu Asp Glu Gln Tyr Phe Ile Glu Pro Leu Lys Asn Thr Thr Glu Asp
165 170 175
Ser Lys His Phe Ser Tyr Glu Asn Gly His Pro His Val Ile Tyr Lys
180 185 190
Lys Ser Ala Leu Gln Gln Arg His Leu Tyr Asp His Ser His Cys Gly
195 200 205
Val Ser Asp Phe Thr Arg Ser Gly Lys Pro Trp Trp Leu Asn Asp Thr
210 215 220
Ile Leu Phe Leu Ile His Tyr Gln Ile Asn Asn Thr His Ile His His
225 230 235 240
Arg Gln Lys Arg Ser Val Ser Ile Glu Arg Phe Val Glu Thr Leu Val
245 250 255
Val Ala Asp Lys Met Met Val Gly Tyr His Gly Arg Lys Asp Ile Glu
260 265 270
His Tyr Ile Leu Ser Val Met Asn Ile Val Ala Lys Leu Tyr Arg Asp
275 280 285
Ser Ser Leu Gly Asn Val Val Asn Ile Ile Val Ala Arg Leu Ile Val
290 295 300

Ala Val Leu Ile Thr Asp Arg Asn Asp Tyr Thr Tyr Gly Asn Lys Ile
305 310 315

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Cys Gly Thr Leu Gly Leu Ala Ser Val Ala Gly Met Cys Glu Pro Glu
    370                 375                 380
Arg Ser Cys Ser Ile Asn Glu Asp Ile Gly Leu Gly Ser Ala Phe Thr
385                 390                 395                 400
Ile Ala His Glu Ile Val His Asn Phe Gly Met Asn His Asp Gly Ile
                405                 410                 415
Gly Asn Ser Cys Gly Arg Lys Val Met Lys Gln Gln Asn Tyr Gly Ser
            420                 425                 430
Ser His Tyr Cys Glu Tyr Gln Ser Phe Phe Leu Val Cys Leu Gln Ser
        435                 440                 445
Arg Xaa His His Gln Leu Phe Arg Glu Val Cys Arg Glu Leu Trp Cys
    450                 455                 460
Leu Ser Lys Ser Asn Arg Cys Val Thr Asn Ser Ile Pro Ala Ala Glu
465                 470                 475                 480
Gly Thr Leu Cys Gln Thr Gly Asn Ile Glu Lys Gly Trp Cys Tyr Gln
                485                 490                 495
Gly Asp Cys Val Pro Phe Gly Thr Trp Pro Gln Ser Ile Asp Gly Gly
            500                 505                 510
Trp Gly Pro Trp Ser Leu Trp Gly Glu Cys Ser Arg Thr Cys Gly Gly
        515                 520                 525
Gly Val Ser Ser Ser Leu Arg His Cys Asp Ser Pro Ala Pro Ser Glu
    530                 535                 540
Val Glu Lys Tyr Cys Leu Gly Glu Arg Lys Arg Tyr Arg Ser Cys Asn
545                 550                 555                 560
Thr Asp Pro Cys Pro Leu Gly Ser Arg Asp Phe Arg Glu Lys Gln Cys
                565                 570                 575
Ala Asp Phe Asp Asn Met Pro Phe Arg Gly Lys Tyr Tyr Asn Trp Lys
            580                 585                 590
Pro Tyr Thr Gly Gly Gly Val Lys Pro Cys Ala Leu Asn Cys Leu Ala
        595                 600                 605
Glu Gly Tyr Asn Phe Tyr Thr Glu Arg Ala Pro Ala Val Ile Asp Gly
    610                 615                 620
Thr Gln Cys Asn Ala Asp Ser Leu Asp Ile Cys Ile Asn Gly Glu Cys
625                 630                 635                 640
Lys His Val Gly Cys Asp Asn Ile Leu Gly Ser Asp Ala Arg Glu Asp
                645                 650                 655
Arg Cys Arg Val Cys Gly Gly Gly Gly Ser Thr Cys Asp Ala Ile Glu
            660                 665                 670
Gly Phe Phe Asn Asp Ser Leu Pro Arg Gly Gly Tyr Met Glu Val Val
        675                 680                 685
Gln Ile Pro Arg Gly Ser Val His Ile Glu Val Arg Glu Val Ala Met
    690                 695                 700
Ser Lys Asn Tyr Ile Ala Leu Lys Ser Glu Gly Asp Asp Tyr Tyr Ile
705                 710                 715                 720
Asn Gly Ala Trp Thr Ile Asp Trp Pro Arg Lys Phe Asp Val Ala Gly
                725                 730                 735
Thr Ala Phe His Tyr Lys Arg Pro Thr Asp Glu Pro Glu Ser Leu Glu
            740                 745                 750
Ala Leu Gly Pro Thr Ser Glu Asn Leu Ile Val Met Val Leu Leu Gln
        755                 760                 765
Glu Gln Asn Leu Gly Ile Arg Tyr Lys Phe Asn Val Pro Ile Thr Arg
    770                 775                 780
Thr Gly Ser Gly Asp Asn Glu Val Gly Phe Thr Trp Asn His Gln Pro
785                 790                 795                 800
Trp Ser Glu Cys Ser Ala Thr Cys Ala Gly Gly Lys Met Pro Thr Arg
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Leu Arg Pro Leu Leu Leu Leu Leu Cys Ala Leu Ala Pro Gly Ala Pro
15 20 25

gga ccc gca cca gga cgt gca acc gag ggc cgg gcg gca ctg gac atc 147
Gly Pro Ala Pro Gly Arg Ala Thr Glu Gly Arg Ala Ala Leu Asp Ile
30 35 40 45

gtg cac ccg gtt cga gtc gac gcg ggg ggc tcc ttc ctg tcc tac gag 195
Val His Pro Val Arg Val Asp Ala Gly Gly Ser Phe Leu Ser Tyr Glu
50 55 60

ctg tgg ccc cgc gca ctg cgc aag cgg gat gta tct gtg cgc cga gac 243
Leu Trp Pro Arg Ala Leu Arg Lys Arg Asp Val Ser Val Arg Arg Asp
65 70 75

gcg ccc gcc ttc tac gag cta caa tac cgc ggg cgc gag ctg cgc ttc 291
Ala Pro Ala Phe Tyr Glu Leu Gln Tyr Arg Gly Arg Glu Leu Arg Phe
80 85 90

aac ctg acc gcc aat cag cac ctg ctg gcg ccc ggc ttt gtg agc gag 339
Asn Leu Thr Ala Asn Gln His Leu Leu Ala Pro Gly Phe Val Ser Glu
95 100 105

acg cgg cgg cgc ggc ggc ctg ggc cgc gcg cac atc cgg gcc cac acc 387
Thr Arg Arg Arg Gly Gly Leu Gly Arg Ala His Ile Arg Ala His Thr
110 115 120 125

ccg gcc tgc cac ctg ctt ggc gag gtg cag gac cct gag ctc gag ggt 435
Pro Ala Cys His Leu Leu Gly Glu Val Gln Asp Pro Glu Leu Glu Gly
130 135 140

ggc ctg gcg gcc atc agc gcc tgc gac ggc ctg aaa ggt gtg ttc cag 483
Gly Leu Ala Ala Ile Ser Ala Cys Asp Gly Leu Lys Gly Val Phe Gln
145 150 155

ctc tcc aac gag gac tac ttt att gag ccc ctg gac agt gcc cag gtc 531
Leu Ser Asn Glu Asp Tyr Phe Ile Glu Pro Leu Asp Ser Ala Pro Ala
160 165 170

cgg cct ggc cac gcc cag ccc cat gtg gtg tac aag cgt cag gcc ccg 579
Arg Pro Gly His Ala Gln Pro His Val Val Tyr Lys Arg Gln Ala Pro
175 180 185

[illegible] [illegible]

[illegible]

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   gtc agc aaa gag aag tgg tgt gag acc ctg gta gta gct gat gcc aaa   771
 5 Val Ser Lys Glu Lys Trp Cys Glu Thr Leu Val Val Ala Asp Ala Lys
           240                 245                 250

   atg gtg gag tac cac gga cag ccg cag gtt gag agc tat gtg ctg acc   819
   Met Val Glu Tyr His Gly Gln Pro Gln Val Glu Ser Tyr Val Leu Thr
10     255                 260                 265

   atc atg aac atg gtg gct ggc ctg ttt cat gac ccc agc att ggg aac   867
   Ile Met Asn Met Val Ala Gly Leu Phe His Asp Pro Ser Ile Gly Asn
   270                 275                 280                 285
15
   ccc atc cac atc acc att gtg cgc ctg gtc ctg ctg gaa gat gag gag   915
   Pro Ile His Ile Thr Ile Val Arg Leu Val Leu Leu Glu Asp Glu Glu
                   290                 295                 300

20 gag gac cta aag atc acg cac cat gca gac aac act ctg aag agc ttc   963
   Glu Asp Leu Lys Ile Thr His His Ala Asp Asn Thr Leu Lys Ser Phe
               305                 310                 315

   tgc aag tgg cag aaa agc atc aac atg aag ggg gat gcc cat ccc ctg  1011
25 Cys Lys Trp Gln Lys Ser Ile Asn Met Lys Gly Asp Ala His Pro Leu
           320                 325                 330

   cac cat gac act gcc atc ctg ctc acc aga aag gac ctg tgt gca gcc  1059
   His His Asp Thr Ala Ile Leu Leu Thr Arg Lys Asp Leu Cys Ala Ala
30     335                 340                 345

   atg aac cgg ccc tgt gag acc ctg gga ctg tcc cat gtg gcg ggc atg  1107
   Met Asn Arg Pro Cys Glu Thr Leu Gly Leu Ser His Val Ala Gly Met
   350                 355                 360                 365
35
   tgc cag ccg cac cgc agc tgc agc atc aac gag gac acg ggc ctg ccg  1155
   Cys Gln Pro His Arg Ser Cys Ser Ile Asn Glu Asp Thr Gly Leu Pro
                   370                 375                 380

40 ctg gcc ttc act gta gcc cac gag ctc ggg cac agt ttt ggc att cag  1203
   Leu Ala Phe Thr Val Ala His Glu Leu Gly His Ser Phe Gly Ile Gln
               385                 390                 395

   cat gac gga agc ggc aat gac tgt gag ccc gtt ggg aaa cga cct ttc  1251
45 His Asp Gly Ser Gly Asn Asp Cys Glu Pro Val Gly Lys Arg Pro Phe
           400                 405                 410

   atc atg tct ccg cag ctg ctg tat gac gcc gct ccc ctg act tgg tcc  1299
   Ile Met Ser Pro Gln Leu Leu Tyr Asp Ala Ala Pro Leu Thr Trp Ser
50     415                 420                 425

   cgc tgc agc cgc cag tat atc acc agg ttc ctt gac cgt ggg tgg ggc  1347
   Arg Cys Ser Arg Gln Tyr Ile Thr Arg Phe Leu Asp Arg Gly Trp Gly
   430                 435                 440                 445
55
   ctg tgc ctg gac gac cct ccg gcc aag gac att atc gac ttc ccc tcg  1395
   Leu Cys Leu Asp Asp Pro Pro Ala Lys Asp Ile Ile Asp Phe Pro Ser
                   450                 455                 460

   [illegible]
               465                 470                 475
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   aca ctc tgg tgc tct gtg ggg acc acc tgt cac tcc aag ctg gat gca   1539
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       495                 500                 505
5
   gct gtg gac ggc acc cgg tgt ggg gag aat aag tgg tgt ctc agt ggg   1587
   Ala Val Asp Gly Thr Arg Cys Gly Glu Asn Lys Trp Cys Leu Ser Gly
   510                 515                 520                 525

10 gag tgc gta ccc gtg ggc ttc cgg ccc gag gcc gtg gat ggt ggc tgg   1635
   Glu Cys Val Pro Val Gly Phe Arg Pro Glu Ala Val Asp Gly Gly Trp
                   530                 535                 540

   tct ggc tgg agc gcc tgg tcc atc tgc tca cgg agc tgt ggc atg ggc   1683
15 Ser Gly Trp Ser Ala Trp Ser Ile Cys Ser Arg Ser Cys Gly Met Gly
               545                 550                 555

   gta cag agc gcc gag cgg cag tgc acg cag cct acg ccc aaa tac aaa   1731
   Val Gln Ser Ala Glu Arg Gln Cys Thr Gln Pro Thr Pro Lys Tyr Lys
20         560                 565                 570

   ggc aga tac tgt gtg ggt gag cgc aag cgc ttc cgc ctc tgc aac ctg   1779
   Gly Arg Tyr Cys Val Gly Glu Arg Lys Arg Phe Arg Leu Cys Asn Leu
       575                 580                 585
25
   cag gcc tgc cct gct ggc cgc ccc tct ttc cgc cac gtc cag tgc agc   1827
   Gln Ala Cys Pro Ala Gly Arg Pro Ser Phe Arg His Val Gln Cys Ser
   590                 595                 600                 605

30 cac ttt gac gct atg ctc tac aag ggc cag ctg cac aca tgg gtg ccc   1875
   His Phe Asp Ala Met Leu Tyr Lys Gly Gln Leu His Thr Trp Val Pro
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   gtg gtc aat gac gtg aac ccc tgc gag ctg cac tgc cgg ccc gcg aat   1923
35 Val Val Asn Asp Val Asn Pro Cys Glu Leu His Cys Arg Pro Ala Asn
               625                 630                 635

   gag tac ttt gcc aag aag ctg cgg gac gcc tgt gtc gat ggc acc ccc   1971
   Glu Tyr Phe Ala Lys Lys Leu Arg Asp Ala Cys Val Asp Gly Thr Pro
40         640                 645                 650

   tgc tac cag gtc cga gcc agc cgg gac ctc tgc atc aac ggc atc tgt   2019
   Cys Tyr Gln Val Arg Ala Ser Arg Asp Leu Cys Ile Asn Gly Ile Cys
       655                 660                 665
45
   aag aac gtg ggc tgt gac ttc gag att gac tct ggt gct atg gag gac   2067
   Lys Asn Val Gly Cys Asp Phe Glu Ile Asp Ser Gly Ala Met Glu Asp
   670                 675                 680                 685

50 cgc tgt cgt gtg tgc cac ggc aac ggt tcc acc tgc cac acc gtg tgc   2115
   Arg Cys Gly Val Cys His Gly Asn Gly Ser Thr Cys His Thr Val Ser
                   690                 695                 700

   ggg acc ttc gag gag gcc gag ggt ctg ggg tat gtg gat gtg ggg ctg   2163
55 Gly Thr Phe Glu Glu Ala Glu Gly Leu Gly Tyr Val Asp Val Gly Leu
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   atc tca gcg ggc gca cgc gag atc cgc atc caa gag ctt gcc gag gct   2211
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Asn Gly Gly Trp Thr Ile Gln Trp Asn Gly Asp Tyr Gln Val Ala Gly
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acc acc ttc aca tac gca cgc agg ggc aac tgg gag aac ctc acg tcc 2355
Thr Thr Phe Thr Tyr Ala Arg Arg Gly Asn Trp Glu Asn Leu Thr Ser
770 775 780

ccg ggt ccc acc aag gag cct gtc tgg atc cag gtg cct gcc tcc cgt 2403
Pro Gly Pro Thr Lys Glu Pro Val Trp Ile Gln Val Pro Ala Ser Arg
785 790 795

ggc cca ggc ggg ggg agc aga ggc gga gtc ccc agg ccc agc acc ctc 2451
Gly Pro Gly Gly Gly Ser Arg Gly Gly Val Pro Arg Pro Ser Thr Leu
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cat ggc agg tct cgt cct gga gga gtg agc cct ggt tca gtc aca gag 2499
His Gly Arg Ser Arg Pro Gly Gly Val Ser Pro Gly Ser Val Thr Glu
815 820 825

cct ggc tct gag cca ggc cct cct gct gcg gcc tct acc tca gtt tcc 2547
Pro Gly Ser Glu Pro Gly Pro Pro Ala Ala Ala Ser Thr Ser Val Ser
830 835 840 845

cca tct tta aaa tgg ccc aat ctt gta gct gca gtt cac aga ggt ggc 2595
Pro Ser Leu Lys Trp Pro Asn Leu Val Ala Ala Val His Arg Gly Gly
850 855 860

tgg ggt caa gct cct tta gga ctg ggt gga tgg aga aga cac ctt gtg 2643
Trp Gly Gln Ala Pro Leu Gly Leu Gly Gly Trp Arg Arg His Leu Val
865 870 875

ctc atg ggc ccc cgc ctg ccc acc cag ctg ctg ttc cag gag agc aac 2691
Leu Met Gly Pro Arg Leu Pro Thr Gln Leu Leu Phe Gln Glu Ser Asn
880 885 890

cct ggg gtg cac tac gag tac acc atc cac agg gag gca ggt ggc cac 2739
Pro Gly Val His Tyr Glu Tyr Thr Ile His Arg Glu Ala Gly Gly His
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gac gag gtc ccg ccg ccc gtg ttc tcc tgg cat tat ggg ccc tgg acc 2787
Asp Glu Val Pro Pro Pro Val Phe Ser Trp His Tyr Gly Pro Trp Thr
910 915 920 925

aag tgc aca gtc acc tgc ggc aga ggt gag aag tgg ggt agg cac agc 2835
Lys Cys Thr Val Thr Cys Gly Arg Gly Glu Lys Trp Gly Arg His Ser
930 935 940

ccc acc tgc agg ggc tta gtg tct gga cag gga cac tgg ctt cag ctc 2883
Pro Thr Cys Arg Gly Leu Val Ser Gly Gln Gly His Trp Leu Gln Leu
945 950 955

cca gct cac tgc tgg gcc acc acg ggt ttg gaa gtt tgc ttc tct gag 2931
Pro Ala His Cys Trp Ala Thr Thr Gly Leu Glu Val Cys Phe Ser Glu
960 965 970

cct cag ttc tcc atc tgt gag atg agg cta gcg att gcc ctg tgt ccc 2979
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Pro Gly Arg Ala Thr Glu Gly Arg Ala Ala Leu Asp Ile Val His Pro
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Val Arg Val Asp Ala Gly Gly Ser Phe Leu Ser Tyr Glu Leu Trp Pro
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Arg Ala Leu Arg Lys Arg Asp Val Ser Val Arg Arg Asp Ala Pro Ala
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Phe Tyr Glu Leu Gln Tyr Arg Gly Arg Glu Leu Arg Phe Asn Leu Thr
                 85                  90                  95

Ala Asn Gln His Leu Leu Ala Pro Gly Phe Val Ser Glu Thr Arg Arg
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Arg Gly Gly Leu Gly Arg Ala His Ile Arg Ala His Thr Pro Ala Cys
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His Leu Leu Gly Glu Val Gln Asp Pro Glu Leu Glu Gly Gly Leu Ala
    130                 135                 140

Ala Ile Ser Ala Cys Asp Gly Leu Lys Gly Val Phe Gln Leu Ser Asn
145                 150                 155                 160

Glu Asp Tyr Phe Ile Glu Pro Leu Asp Ser Ala Pro Ala Arg Pro Gly
                165                 170                 175

His Ala Gln Pro His Val Val Tyr Lys Arg Gln Ala Pro Glu Arg Leu
            180                 185                 190

Ala Gln Arg Gly Asp Ser Ser Ala Pro Ser Thr Cys Gly Val Gln Val
        195                 200                 205

Tyr Pro Glu Leu Glu Ser Arg Arg Glu Arg Trp Glu Gln Arg Gln Gln
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Trp Arg Arg Pro Arg Leu Arg Arg Leu His Gln Arg Ser Val Ser Lys
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Glu Lys Thr Thr Glu Thr Leu Val Val Ala Asn Ala Lys Met Val Glu

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Lys Ile Thr His His Ala Asp Asn Thr Leu Lys Ser Phe Cys Lys Trp
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Gln Lys Ser Ile Asn Met Lys Gly Asp Ala His Pro Leu His His Asp
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Thr Ala Ile Leu Leu Thr Arg Lys Asp Leu Cys Ala Ala Met Asn Arg
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Pro Cys Glu Thr Leu Gly Leu Ser His Val Ala Gly Met Cys Gln Pro
355 360 365

His Arg Ser Cys Ser Ile Asn Glu Asp Thr Gly Leu Pro Leu Ala Phe
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Thr Val Ala His Glu Leu Gly His Ser Phe Gly Ile Gln His Asp Gly
385 390 395 400

Ser Gly Asn Asp Cys Glu Pro Val Gly Lys Arg Pro Phe Ile Met Ser
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Pro Gln Leu Leu Tyr Asp Ala Ala Pro Leu Thr Trp Ser Arg Cys Ser
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Arg Gln Tyr Ile Thr Arg Phe Leu Asp Arg Gly Trp Gly Leu Cys Leu
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Asp Asp Pro Pro Ala Lys Asp Ile Ile Asp Phe Pro Ser Val Pro Pro
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Gly Val Leu Tyr Asp Val Ser His Gln Cys Arg Leu Gln Tyr Gly Ala
465 470 475 480

Tyr Ser Ala Phe Cys Glu Asp Met Asp Asn Val Cys His Thr Leu Trp
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Cys Ser Val Gly Thr Thr Cys His Ser Lys Leu Asp Ala Ala Val Asp
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Gly Thr Arg Cys Gly Glu Asn Lys Trp Cys Leu Ser Gly Glu Cys Val
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Pro Val Gly Phe Arg Pro Glu Ala Val Asp Gly Gly Trp Ser Gly Trp
530 535 540

Ser Ala Trp Ser Ile Cys Ser Arg Ser Cys Gly Met Gly Val Gln Ser
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Ala Glu Arg Gln Cys Thr Gln Pro Thr Pro Lys Tyr Lys Gly Arg Tyr
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Cys Val Gly Glu Arg Lys Arg Phe Arg Leu Cys Asn Leu Gln Ala Cys
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Pro Ala Gly Arg Ser Ser Phe Ala His Val Glu Cys Ser His Phe Asn

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Ala Lys Lys Leu Arg Asp Ala Cys Val Asp Gly Thr Pro Cys Tyr Gln
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Val Arg Ala Ser Arg Asp Leu Cys Ile Asn Gly Ile Cys Lys Asn Val
            660                 665                 670

Gly Cys Asp Phe Glu Ile Asp Ser Gly Ala Met Glu Asp Arg Cys Gly
        675                 680                 685

Val Cys His Gly Asn Gly Ser Thr Cys His Thr Val Ser Gly Thr Phe
    690                 695                 700

Glu Glu Ala Glu Gly Leu Gly Tyr Val Asp Val Gly Leu Ile Pro Ala
705                 710                 715                 720

Gly Ala Arg Glu Ile Arg Ile Gln Glu Val Ala Glu Ala Ala Asn Phe
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Leu Ala Leu Arg Ser Glu Asp Pro Glu Lys Tyr Phe Leu Asn Gly Gly
            740                 745                 750

Trp Thr Ile Gln Trp Asn Gly Asp Tyr Gln Val Ala Gly Thr Thr Phe
        755                 760                 765

Thr Tyr Ala Arg Arg Gly Asn Trp Glu Asn Leu Thr Ser Pro Gly Pro
    770                 775                 780

Thr Lys Glu Pro Val Trp Ile Gln Val Pro Ala Ser Arg Gly Pro Gly
785                 790                 795                 800

Gly Gly Ser Arg Gly Gly Val Pro Arg Pro Ser Thr Leu His Gly Arg
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Ser Arg Pro Gly Gly Val Ser Pro Gly Ser Val Thr Glu Pro Gly Ser
            820                 825                 830

Glu Pro Gly Pro Pro Ala Ala Ala Ser Thr Ser Val Ser Pro Ser Leu
        835                 840                 845

Lys Trp Pro Asn Leu Val Ala Ala Val His Arg Gly Gly Trp Gly Gln
    850                 855                 860

Ala Pro Leu Gly Leu Gly Gly Trp Arg Arg His Leu Val Leu Met Gly
865                 870                 875                 880

Pro Arg Leu Pro Thr Gln Leu Leu Phe Gln Glu Ser Asn Pro Gly Val
                885                 890                 895

His Tyr Gln Tyr Thr Ile His Arg Glu Ala Gly Gly His Asp Glu Val
            900                 905                 910

Pro Pro Pro Val Phe Ser Trp His Tyr Gly Pro Trp Thr Lys Cys Thr
        915                 920                 925

Val Thr Cys Gly Arg Gly Glu Lys Trp Gly Arg His Ser Pro Thr Cys
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ttcctggaca gagcgacccg gccgcctcgg gccaccagca cctgcccgcg cgcggcgatc 240

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Met Leu Arg Asp Pro Thr
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Thr Thr Gly Trp Pro Pro Leu Leu Leu Leu Leu Gln Leu Pro Pro
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Pro Pro Leu Val Cys Gly Ala Pro Ala Gly Pro Gly Thr Gly Ala Gln
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Ala Ser Glu Leu Val Val Pro Thr Arg Leu Pro Gly Ser Ala Ser Glu
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ctc gcc ttc cac ctg tcc gcc ttc ggc cag ggc ttc gtg ctg cgc ctg 487
Leu Ala Phe His Leu Ser Ala Phe Gly Gln Gly Phe Val Leu Arg Leu
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gcg cct gac gcc agc ttc ctg gcg ccg gaa ttc aag atc gag cgc ctc 535
Ala Pro Asp Ala Ser Phe Leu Ala Pro Glu Phe Lys Ile Glu Arg Leu
75 80 85

ggg ggc tcg agc gcg gcg gcc ggg ggc gag ccg gga ctg cgc ggc tgc 583
Gly Gly Ser Ser Ala Ala Ala Gly Gly Glu Pro Gly Leu Arg Gly Cys
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ttc ttc tct ggc aca gtg aat gga gaa cgg gag tcg ctg gcg gcg atg 631
Phe Phe Ser Gly Thr Val Asn Gly Glu Arg Glu Ser Leu Ala Ala Met
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agc tgt gtc gcg ggc tgg agc ggc tcg ttc ttg ctg gca ggc gag gag 679
Ser Cys Val Ala Gly Trp Ser Gly Ser Phe Leu Leu Ala Gly Glu Glu
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Ala Ala Leu Ala Gly Val Ile Gly Thr Ala Ala Val Leu Asp Ile Gly Val Asn Leu
135 140 145

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   gct gcc gcc gaa gtt ttc ccc ctc cct caa gga ctg gag tgg gag gtg   823
   Ala Ala Ala Glu Val Phe Pro Leu Pro Gln Gly Leu Glu Trp Glu Val
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   gag atg ggt aat ggg cag gga cag gag aga agt gac aac gaa gag gac   871
   Glu Met Gly Asn Gly Gln Gly Gln Glu Arg Ser Asp Asn Glu Glu Asp
           185                 190                 195

10 aag aag cag gac aag gag ggg ttg ctc aaa gag aca gaa gac tcc cgc   919
   Lys Lys Gln Asp Lys Glu Gly Leu Leu Lys Glu Thr Glu Asp Ser Arg
       200                 205                 210

   aaa gtg cca cca ccc ttc gga tcc aaa act aga agc aag agg ttt gtg   967
15 Lys Val Pro Pro Pro Phe Gly Ser Lys Thr Arg Ser Lys Arg Phe Val
   215                 220                 225                 230

   tcc gag gct cgc ttc gtg gaa aca ctt ctg gtg gct gat gcg tcc atg  1015
   Ser Glu Ala Arg Phe Val Glu Thr Leu Leu Val Ala Asp Ala Ser Met
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   gct gcc ttc tat ggg acc gac ctg cag aac cac atc ctc acg gtg atg  1063
   Ala Ala Phe Tyr Gly Thr Asp Leu Gln Asn His Ile Leu Thr Val Met
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   tca atg gca gcc cga atc tac aag cac ccg agc atc agg aac tcc gtc  1111
   Ser Met Ala Ala Arg Ile Tyr Lys His Pro Ser Ile Arg Asn Ser Val
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30 aac ctt gtg gtg gtg aaa gtg cta ata gtg gaa aaa gaa aga tgg ggc  1159
   Asn Leu Val Val Val Lys Val Leu Ile Val Glu Lys Glu Arg Trp Gly
       280                 285                 290

   ccg gaa gtg tcc gac aac ggg ggg ctc aca ctg cgc aac ttc tgc agc  1207
35 Pro Glu Val Ser Asp Asn Gly Gly Leu Thr Leu Arg Asn Phe Cys Ser
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   tgg caa cgg cgt ttc aac aag ccc agt gac cgc cac ccg gag cac tat  1255
   Trp Gln Arg Arg Phe Asn Lys Pro Ser Asp Arg His Pro Glu His Tyr
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   gac act gcc atc ttg ttc acc aga cag aac ttc tgt ggg aag gga gag  1303
   Asp Thr Ala Ile Leu Phe Thr Arg Gln Asn Phe Cys Gly Lys Gly Glu
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   cag tgt gac acc ctg ggg atg gca gac gtt cgc acc atc tgt gac ccc  1351
   Gln Cys Asp Thr Leu Gly Met Ala Asp Val Gly Thr Ile Cys Asp Pro
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50 gac aag agc tgt tca gtg atc aag gat gag gga ctg cag gca gcc tac  1399
   Asp Lys Ser Cys Ser Val Ile Lys Asp Glu Gly Leu Gln Ala Ala Tyr
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   acc ctg gcc cat gag cta ggg cac gtt ctc agc atg ccc cat gat gat  1447
55 Thr Leu Ala His Glu Leu Gly His Val Leu Ser Met Pro His Asp Asp
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   tct aag ccc tgt gtg aga ttg ttt gac cct atg ggc aac tac ctc atg  1495
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   Cys Ser Ala Val Tyr Leu Thr Glu Leu Leu Asp Asp Gly His Gly Asp
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   tgt ctt ctg gat gcc ccc acc tcg gtt ctg ccc ctc ccc aca ggc ctc   1639
 5 Cys Leu Leu Asp Ala Pro Thr Ser Val Leu Pro Leu Pro Thr Gly Leu
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   ccg ggc cac agc acc ctc tac gag ctg gac cag cag tgc aag cag atc   1687
   Pro Gly His Ser Thr Leu Tyr Glu Leu Asp Gln Gln Cys Lys Gln Ile
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   ttt ggg cct gat ttc cga cac tgc ccc aac acc tct gtg gag gac atc   1735
   Phe Gly Pro Asp Phe Arg His Cys Pro Asn Thr Ser Val Glu Asp Ile
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   tgt gtc cag ctc tgt gcc cgt cat cgg gat agt gat gag ccc att tgc   1783
   Cys Val Gln Leu Cys Ala Arg His Arg Asp Ser Asp Glu Pro Ile Cys
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20 cac aca aag aat ggt agc ctg ctc tgg gct gat ggt aca ccc tgt ggc   1831
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   cct ggg cac ctg tgc ctg gat ggt agc tgt gta ctc aag gag gat gtg   1879
25 Pro Gly His Leu Cys Leu Asp Gly Ser Cys Val Leu Lys Glu Asp Val
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   gag aat ccc aag gct gtg gta gat gga gac tgg ggt ccc tgg aga ccc   1927
   Glu Asn Pro Lys Ala Val Val Asp Gly Asp Trp Gly Pro Trp Arg Pro
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   tgg gga caa tgt tct cgc acc tgt ggt gga ggg ata caa ttc tcg aac   1975
   Trp Gly Gln Cys Ser Arg Thr Cys Gly Gly Gly Ile Gln Phe Ser Asn
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   cgt gaa tgt gat aat cca atg cct cag aat gga gga aga ttt tgc ctg   2023
   Arg Glu Cys Asp Asn Pro Met Pro Gln Asn Gly Gly Arg Phe Cys Leu
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40 ggt gaa aga gtc aag tac caa tca tgc aac aca gag gaa tgt cca cca   2071
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   aac gga aaa agc ttc cgg gag cag cag tgt gag aaa tat aat gcc tac   2119
45 Asn Gly Lys Ser Phe Arg Glu Gln Gln Cys Glu Lys Tyr Asn Ala Tyr
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   aac cac act gac ctg gat ggg aat ttc ctg cag tgg gtc ccc aag tat   2167
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   tca gga gtg tcc ccc cga gac cga tgc aag ctg ttt tgc aga gcc cgt   2215
   Ser Gly Val Ser Pro Arg Asp Arg Cys Lys Leu Phe Cys Arg Ala Arg
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   ggg agg agt gag ttc aaa gtg ttt gaa gct aag gtg atc gat ggc act   2263
   Gly Arg Ser Glu Phe Lys Val Phe Glu Ala Lys Val Ile Asp Gly Thr
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   Cys                 665                 670
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   Cys Gly Val Cys Gly Gly Lys Gly Thr Ala Cys Arg Lys Ile Ser Gly
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   tct ttc acc ccc ttc agt tat ggc tac aat gac att gtc acc atc cca   2448
   Ser Phe Thr Pro Phe Ser Tyr Gly Tyr Asn Asp Ile Val Thr Ile Pro
                   715                 720                 725

10 gct ggt gcc aca aac att gat gtg aaa cag cgg agt cac cca ggg gtc   2496
   Ala Gly Ala Thr Asn Ile Asp Val Lys Gln Arg Ser His Pro Gly Val
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   agg aac gac ggc agc tac ctg gcg ctg aag aca gcc aat ggg cag tac   2544
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           745                 750                 755

   ctg ctc aat ggt aac ctg gcc atc tct gcc ata gag caa gac atc ttg   2592
   Leu Leu Asn Gly Asn Leu Ala Ile Ser Ala Ile Glu Gln Asp Ile Leu
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   gtg aag ggg acc atc ctg aag tat agt ggc tcc atg gct acc ctg gag   2640
   Val Lys Gly Thr Ile Leu Lys Tyr Ser Gly Ser Met Ala Thr Leu Glu
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   cgg ctg cag agc ttc cag gcc ctg cct gag cct ctt aca gta cag ctc   2688
   Arg Leu Gln Ser Phe Gln Ala Leu Pro Glu Pro Leu Thr Val Gln Leu
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30 ctg act gtg tct ggt gag gtc ttc cct cca aaa gtc aga tat acc ttc   2736
   Leu Thr Val Ser Gly Glu Val Phe Pro Pro Lys Val Arg Tyr Thr Phe
               810                 815                 820

   ttt gtc ccc aat gac atg gac ttc agc gtg cag aat agc aag gaa aga   2784
35 Phe Val Pro Asn Asp Met Asp Phe Ser Val Gln Asn Ser Lys Glu Arg
           825                 830                 835

   gca acc acc aac atc att cag tca ctg ccc tct gcg gag tgg gtt ctg   2832
   Ala Thr Thr Asn Ile Ile Gln Ser Leu Pro Ser Ala Glu Trp Val Leu
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   gga gac tgg tct gaa tgt ccg agc acg tgc aga ggt agc tgg cag cgg   2880
   Gly Asp Trp Ser Glu Cys Pro Ser Thr Cys Arg Gly Ser Trp Gln Arg
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   cgg act gtg gaa tgc agg gac ccc tca ggt cag gcc tct gac acc tgt   2928
   Arg Thr Val Glu Cys Arg Asp Pro Ser Gly Gln Ala Ser Asp Thr Cys
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50 gat gag gct ttg aaa cct gag gat gcc aag ccc tgt gga agc cag ccg   2976
   Asp Glu Ala Leu Lys Pro Glu Asp Ala Lys Pro Cys Gly Ser Gln Pro
               890                 895                 900

   tgt ccc ctc tgatccgctt ggtggaaatc tcttaggctt atggatttgg           3032
55 Cys Pro Leu
           905
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		20					25					30			
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Gly	Phe	Val	Leu	Arg	Leu	Ala	Pro	Asp	Ala	Ser	Phe	Leu	Ala	Pro	Glu
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Pro	Gly	Leu	Arg	Gly	Cys	Phe	Phe	Ser	Gly	Thr	Val	Asn	Gly	Glu	Arg
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Val	Ala	Asp	Ala	Ser	Met	Ala	Ala	Phe	Tyr	Gly	Thr	Asp	Leu	Gln	Asn

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His Ile Leu Thr Val Met Ser Met Ala Ala Arg Ile Tyr Lys His Pro
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275 280 285

Glu Lys Glu Arg Trp Gly Pro Glu Val Ser Asp Asn Gly Gly Leu Thr
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Pro Ser Ile Lys Asn Ser Ile Asn Leu Met Val Val Lys Val Leu Ile
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Asp Arg His Pro Glu His Tyr Asp Thr Ala Ile Leu Leu Thr Arg Gln
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Ile Gly Thr Ile Cys Asp Pro Asn Lys Ser Cys Ser Val Ile Glu Asp
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Arg Lys Asp Arg Leu His Pro Arg Gln Val Lys Leu Leu Glu Thr Leu
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Pro Phe Pro Thr Asn Val His Phe Lys Arg Thr Arg Arg Ser Ile Asn
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tct gcc act gac ccc tgg cct gcc ttc gcc tcc tcc tct tcc tcc tct   287
Ser Ala Thr Asp Pro Trp Pro Ala Phe Ala Ser Ser Ser Ser Ser Ser
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acc tcc tcc cag gcg cat tac cgc ctc tct gcc ttc ggc cag cag ttt   335
Thr Ser Ser Gln Ala His Tyr Arg Leu Ser Ala Phe Gly Gln Gln Phe
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Leu Phe Asn Leu Thr Ala Asn Ala Gly Phe Ile Ala Pro Leu Phe Thr
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gtc acc ctc ctt ggg acg ccc ggg gtg aat cag acc aag ttt tat tcc   431
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Glu Glu Glu Ala Glu Leu Lys His Cys Phe Tyr Lys Arg Leu Cys Gln
    145                 150                 155

tac caa ctc cga gca cac ggc cgt cat cag cct ctg ctc agg aat gaa   527
Tyr Gln Leu Arg Ala His Gly Arg His Gln Pro Leu Leu Arg Asn Glu
160                 165                 170                 175

cac aaa aat agg cac agt aaa gac aag aag aaa acc aga gca aga aaa   575
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   cca cgg ttt gta gaa gtc ttg gtg gtg gca gac aac aga atg gtt tca   767
   Pro Arg Phe Val Glu Val Leu Val Val Ala Asp Asn Arg Met Val Ser
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   tac cat gga gaa aac ctt caa cac tat att tta act tta atg tca att   815
   Tyr His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu Met Ser Ile
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15 gta gcc tct atc tat aaa gac cca agt att gga aat tta att aat att   863
   Val Ala Ser Ile Tyr Lys Asp Pro Ser Ile Gly Asn Leu Ile Asn Ile
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   gtt att gtg aac tta att gtg att cat aat gaa cag gat ggg cct tcc   911
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   Ile Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Phe Cys Gln Trp Gln
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   cat tcg aac agt cca ggt gga atc cat cat gat act gct gtt ctc tta  1007
   His Ser Asn Ser Pro Gly Gly Ile His His Asp Thr Ala Val Leu Leu
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35 ctg gct gaa ctg gga acc att tgt gat ccc tat aga agt tgt tct att  1103
   Leu Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg Ser Cys Ser Ile
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   agt gaa gat agt gga ttg agt aca gct ttt acg atc gcc cat gag ctg  1151
40 Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile Ala His Glu Leu
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   Gly His Val Phe Asn Met Pro His Asp Asp Asn Asn Lys Cys Lys Glu
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   Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro Thr Leu Asn Phe
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55 gag ttt tta gac act ggt tat ggc gag tgt ttg ctt aat gaa cct gaa  1343
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 5  gta cac aaa ggc tgc cgg act cag cac aca ccc tgg gcc gat ggg acg   1535
    Val His Lys Gly Cys Arg Thr Gln His Thr Pro Trp Ala Asp Gly Thr
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    gag tgc gag cct gga aag cac tgc aag nat gga ttt tgt gtt ccc aaa   1583
10  Glu Cys Glu Pro Gly Lys His Cys Lys Xaa Gly Phe Cys Val Pro Lys
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    gaa atg gat gtc ccc gtg aca gat gga tcc tgg gga agt tgg agt ccc   1631
    Glu Met Asp Val Pro Val Thr Asp Gly Ser Trp Gly Ser Trp Ser Pro
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    ttt gga acc tgc tcc aga aca tgt gga ggg ggc atc aaa aca gcc att   1679
    Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile Lys Thr Ala Ile
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    cga gag tgc aac aga cca gaa cca aaa aat ggt gga aaa tac tgt gta   1727
    Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly Lys Tyr Cys Val
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25  gga cgt aga atg aaa ttt aag tcc tgc aac acg gag cca tgt ctc aag   1775
    Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu Pro Cys Leu Lys
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    cat ttt aac atc aac ggt ctg ctt ccc aat gtg cgc tgg gtc cct aaa   1871
    His Phe Asn Ile Asn Gly Leu Leu Pro Asn Val Arg Trp Val Pro Lys
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    tac agt gga att ctg atg aag gac cgg tgc aag ttg ttc tgc aga gtg   1919
    Tyr Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu Phe Cys Arg Val
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    gca ggg aac aca gcc tac tat cag ctt cga gac aga gtg ata gat gga   1967
    Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg Val Ile Asp Gly
    640                 645                 650                 655

45  act cct tgt ggc cag gac aca aat gat atc tgt gtc cag ggc ctt tgt   2015
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50  Arg Glu Ala Gly Cys Asp His Val Leu Asn Ser Lys Ala Arg Arg Asp
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    Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr Val Val Arg Ile

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   Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser Glu Thr Ala Val
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   Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val Arg Tyr Ser Phe
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   Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr Val Ser Asp Gln
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   aga tgc gat cgg ctg ccc cag cct gga cac att act gaa ccc tgt ggt   2639
   Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr Glu Pro Cys Gly
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35 aca ggc tgt gac ctg agg tgg cat gtt gcc agc agg agt gaa tgt agt   2687
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   880                 885                 890                 895

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   tat agc agg ctg gat ggg aag act gag aag gtt gat gat ggt ttt tgc   2783
   Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp Asp Gly Phe Cys
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   agt agt cat ccc aaa cca agc aac cgt gaa aaa tgt tca ggg gaa tgt   2831
   Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys Ser Gly Glu Cys
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   aac acg ggt ggc tgg cgc tat tct gcc tgg act gaa tgt tca aaa agc   2879
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cct gag acc aag cca aca tct atg cag act tgt cag cag ccg gaa tgt   3167
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   Pro Asp Arg Glu Gln Cys Asn Thr His Ala Cys Pro His Asp Ala Ala
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   Trp Ser Thr Gly Pro Trp Ser Ser Cys Ser Val Ser Cys Gly Arg Gly
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35 cat aaa caa cga aat gtt tac tgc atg gca aaa gat gga agc cat tta   4271
   His Lys Gln Arg Asn Val Tyr Cys Met Ala Lys Asp Gly Ser His Leu
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   gaa agt gat tac tgt aag cac ctg gct aag cca cat ggg cac aga aag   4319
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   tgc cga gga gga aga tgc ccc aaa tgg aaa gct ggc gtt tgg agt cag   4367
   Cys Arg Gly Gly Arg Cys Pro Lys Trp Lys Ala Gly Ala Trp Ser Gln
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   tgc tct gtg tcc atg ggc cga ggc gta cag cag agg cat gtg ggc tgt   4415
   Cys Ser Val Ser Met Gly Arg Gly Val Gln Gln Arg His Val Gly Cys
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   cag atc gga aca cac aaa ata gcc aga gag acc gag tgc aac cca tac   4463
   Gln Ile Gly Thr His Lys Ile Ala Arg Glu Thr Glu Cys Asn Pro Tyr
              1475                1480                1485

55 acc aga ccg gag tcg gaa tgc gaa tgc caa ggc cca cgg tgt ccc ctt   4511
   Thr Arg Pro Glu Ser Glu Cys Glu Cys Gln Gly Pro Arg Cys Pro Leu
         1490                1495                1500
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   gag gtg cat ggg gca cgc tgt gac gtg agc aag cgg ccg gtg gac cgt   4655
   Glu Val His Gly Ala Arg Cys Asp Val Ser Lys Arg Pro Val Asp Arg
                  1540                1545                1550

 5 gaa agc tgt agt ttg caa ccc tgc gag tat gtc tgg act aca gga gaa   4703
   Glu Ser Cys Ser Leu Gln Pro Cys Glu Tyr Val Trp Thr Thr Gly Glu
              1555                1560                1565

   tgg tca gag tgc tca gtg acc tgt gga aaa ggc tac aaa caa agg ctt   4751
10 Trp Ser Glu Cys Ser Val Thr Cys Gly Lys Gly Tyr Lys Gln Arg Leu
          1570                1575                1580

   gtc tcg tgc agc gag att tac acc ggg aaa gag aat tat gaa tac agc   4799
   Val Ser Cys Ser Glu Ile Tyr Thr Gly Lys Glu Asn Tyr Glu Tyr Ser
15    1585                1590                1595

   tac caa acc acc atc aac tgc cca ggc acg cag ccc ccc agt gtt cac   4847
   Tyr Gln Thr Thr Ile Asn Cys Pro Gly Thr Gln Pro Pro Ser Val His
   1600                1605                1610                1615
20
   ccc tgt tac ctg agg gag tgc cct gtc tcg gcc acc tgg aga gtt ggc   4895
   Pro Cys Tyr Leu Arg Glu Cys Pro Val Ser Ala Thr Trp Arg Val Gly
                  1620                1625                1630

25 aac tgg ggg agc tgc tca gtg tct tgt ggt gtt gga gtg atg cag aga   4943
   Asn Trp Gly Ser Cys Ser Val Ser Cys Gly Val Gly Val Met Gln Arg
              1635                1640                1645

   tct gtg caa tgt tta acc aat gag gac caa ccc agc cac tta tgc cac   4991
30 Ser Val Gln Cys Leu Thr Asn Glu Asp Gln Pro Ser His Leu Cys His
          1650                1655                1660

   act gat ctg aag cca gaa gaa cga aaa acc tgc cgt aat gtc tat aac   5039
   Thr Asp Leu Lys Pro Glu Glu Arg Lys Thr Cys Arg Asn Val Tyr Asn
35    1665                1670                1675

   tgt gag tta ccc cag aat tgc aag gag gta aaa aga ctt aaa ggt gcc   5087
   Cys Glu Leu Pro Gln Asn Cys Lys Glu Val Lys Arg Leu Lys Gly Ala
   1680                1685                1690                1695
40
   agt gaa gat ggt gaa tat ttc ctg atg att aga gga aag ctt ctg aag   5135
   Ser Glu Asp Gly Glu Tyr Phe Leu Met Ile Arg Gly Lys Leu Leu Lys
                  1700                1705                1710

45 ata ttc tgt gcg ggg atg cac tct gat cac ccc aaa gag tac gtg aca   5183
   Ile Phe Cys Ala Gly Met His Ser Asp His Pro Lys Glu Tyr Val Thr
              1715                1720                1725

   ctg gtg cat gga gac tct gag aat ttc tcc gag gtt tat ggg gac agg   5231
50 Leu Val His Gly Asp Ser Glu Asn Phe Ser Glu Val Tyr Gly His Arg
          1730                1735                1740

   tta cac aac cca aca gaa tgt ccc tat aac ggg agc cgg cgc gat gac   5279
   Leu His Asn Pro Thr Glu Cys Pro Tyr Asn Gly Ser Arg Arg Asp Asp
55    1745                1750                1755

   tgc caa tgt ggg aag gat tac agg gcc gct ggg ttt tcc agt ttt cag   5327
   Cys Gln Cys Gly Lys Asp Tyr Arg Ala Ala Gly Phe Ser Ser Phe Gln

   gaa ttt gtc agg aga tgt gaa ggg cac gtc ctc gcc gtc ttc gac aac   5375
   Glu Phe Ala Arg Thr Ser Glu Gly His Val Leu Ala Val Phe Asp Asn
```

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                1795                1800                1805

   ggg gat tgc tac agc gct gcc aag tgc cca cag ggt cgt ttt agc atc   5471
   Gly Asp Cys Tyr Ser Ala Ala Lys Cys Pro Gln Gly Arg Phe Ser Ile
 5        1810                1815                1820

   aac ctt tat gga acc ggc ttg tct tta act gaa tct gcc aga tgg ata   5519
   Asn Leu Tyr Gly Thr Gly Leu Ser Leu Thr Glu Ser Ala Arg Trp Ile
      1825                1830                1835
10
   tca caa ggg aat tat gct gtc tct gac atc aag aag tcg ccg gat ggt   5567
   Ser Gln Gly Asn Tyr Ala Val Ser Asp Ile Lys Lys Ser Pro Asp Gly
   1840                1845                1850                1855

15 acc cga gtc gta ggg aaa tgc ggt ggt tac tgt gga aaa tgc act cca   5615
   Thr Arg Val Val Gly Lys Cys Gly Gly Tyr Cys Gly Lys Cys Thr Pro
                  1860                1865                1870

   tcc tct ggt act ggc ctg gag gtg cga gtt tta tagctaaggt gttttgaaga 5668
20 Ser Ser Gly Thr Gly Leu Glu Val Arg Val Leu
              1875                1880

   ggaagccatt atggatggat gaaggatagt aatgcaatac ctccacctta atttgggtgc 5728

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   catatacata tataca                                                 5804


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   Lys Asp Arg Leu His Pro Arg Gln Val Lys Leu Leu Glu Thr Leu Ser
            35                  40                  45

45 Glu Tyr Glu Ile Val Ser Pro Ile Arg Val Asn Ala Leu Gly Glu Pro
        50                  55                  60

   Phe Pro Thr Asn Val His Phe Lys Arg Thr Arg Arg Ser Ile Asn Ser
    65                  70                  75                  80
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   Ala Thr Asp Pro Trp Pro Ala Phe Ala Ser Ser Ser Ser Ser Ser Thr
                85                  90                  95

   Ser Ser Gln Ala His Tyr Arg Leu Ser Ala Phe Gly Gln Gln Phe Leu
55              100                 105                 110

   Phe Asn Leu Thr Ala Asn Ala Gly Phe Ile Ala Pro Leu Phe Thr Val
            115                 120                 125
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                                                                  .

   Gln Leu Arg Ala His Gly Arg His Ser Ile Leu Leu Arg Asn Glu His
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                    165                 170                 175

Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg Ala Arg Lys Trp
            180                 185                 190

Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala Leu Asn Ser Gly
        195                 200                 205

Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys Thr Asp Asn Thr
    210                 215                 220

Arg Glu Lys Arg Thr His Arg Arg Thr Lys Arg Phe Leu Ser Tyr Pro
225                 230                 235                 240

Arg Phe Val Glu Val Leu Val Val Ala Asp Asn Arg Met Val Ser Tyr
                245                 250                 255

His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu Met Ser Ile Val
            260                 265                 270

Ala Ser Ile Tyr Lys Asp Pro Ser Ile Gly Asn Leu Ile Asn Ile Val
        275                 280                 285

Ile Val Asn Leu Ile Val Ile His Asn Glu Gln Asp Gly Pro Ser Ile
    290                 295                 300

Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Phe Cys Gln Trp Gln His
305                 310                 315                 320

Ser Asn Ser Pro Gly Gly Ile His His Asp Thr Ala Val Leu Leu Thr
                325                 330                 335

Arg Gln Asp Ile Cys Arg Ala His Asp Lys Cys Asp Thr Leu Gly Leu
            340                 345                 350

Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg Ser Cys Ser Ile Ser
        355                 360                 365

Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile Ala His Glu Leu Gly
    370                 375                 380

His Val Phe Asn Met Pro His Asp Asp Asn Asn Lys Cys Lys Glu Glu
385                 390                 395                 400

Gly Val Lys Ser Pro Gln His Val Met Ala Pro Thr Leu Asn Phe Tyr
                405                 410                 415

Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg Lys Tyr Ile Thr Glu
            420                 425                 430

Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn Glu Pro Glu Ser
        435                 440                 445

Arg Pro Tyr Pro Leu Pro Val Gln Leu Pro Gly Ile Leu Tyr Asn Val
    450                 455                 460

Asn Lys Gln Xaa Glu Leu Ile Phe Gly Pro Gly Ser Gln Val Cys Pro
465                 470                 475                 480
```

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          515                 520                 525

   Met Asp Val Pro Val Thr Asp Gly Ser Trp Gly Ser Trp Ser Pro Phe
       530                 535                 540
 5
   Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile Lys Thr Ala Ile Arg
   545                 550                 555                 560

   Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly Lys Tyr Cys Val Gly
10                 565                 570                 575

   Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu Pro Cys Leu Lys Gln
              580                 585                 590

15 Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His Phe Asp Gly Lys His
          595                 600                 605

   Phe Asn Ile Asn Gly Leu Leu Pro Asn Val Arg Trp Val Pro Lys Tyr
       610                 615                 620
20
   Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu Phe Cys Arg Val Ala
   625                 630                 635                 640

   Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg Val Ile Asp Gly Thr
25                 645                 650                 655

   Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val Gln Gly Leu Cys Arg
              660                 665                 670

30 Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys Ala Arg Arg Asp Lys
          675                 680                 685

   Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys Lys Thr Val Ala Gly
       690                 695                 700
35
   Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr Val Val Arg Ile Pro
   705                 710                 715                 720

   Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His Ser Phe Ser Gly Glu
40                 725                 730                 735

   Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser Ser Lys Gly Glu Phe
              740                 745                 750

45 Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala Lys Arg Glu Ile Arg
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   Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser Glu Thr Ala Val Glu
       770                 775                 780
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   Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu Leu Leu Leu Gln Val
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   Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val Arg Tyr Ser Phe Asn
55                 805                 810                 815

   Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr Trp Asn Ser His Leu
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   Ala Asp Arg Leu Ile Ala Asp Asn Pro Ile Ile Gly Phe Tyr Ala
          835                 840                 845
```

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865                 870                 875                 880

Gly Cys Asp Leu Arg Trp His Val Ala Ser Arg Ser Glu Cys Ser Ala
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Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile Tyr Cys Ala Lys Tyr
            900                 905                 910

Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp Asp Gly Phe Cys Ser
        915                 920                 925

Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys Ser Gly Glu Cys Asn
    930                 935                 940

Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu Cys Ser Lys Ser Cys
945                 950                 955                 960

Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile Cys Val Asn Thr Arg Asn
                965                 970                 975

Asp Val Leu Asp Asp Ser Lys Cys Thr His Gln Glu Lys Val Thr Ile
            980                 985                 990

Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln Trp Lys Ser Gly Asp Trp
        995                1000                1005

Ser Glu Cys Leu Val Thr Cys Gly Lys Gly His Lys His Ser Gln Val
   1010                1015                1020

Trp Cys Gln Phe Gly Glu Asp Arg Leu Asn Asp Arg Met Cys Asp Pro
1025                1030                1035                1040

Glu Thr Lys Pro Thr Ser Met Gln Thr Cys Gln Gln Pro Glu Cys Ala
                1045                1050                1055

Ser Trp Gln Ala Gly Pro Trp Val Gln Cys Ser Val Thr Cys Gly Gln
            1060                1065                1070

Gly Tyr Gln Leu Arg Ala Val Lys Cys Ile Ile Gly Thr Tyr Met Ser
        1075                1080                1085

Val Val Asp Asp Asn Asp Cys Asn Ala Ala Thr Arg Pro Thr Asp Thr
   1090                1095                1100

Gln Asp Cys Glu Leu Pro Ser Cys His Pro Pro Pro Ala Ala Pro Glu
1105                1110                1115                1120

Thr Arg Arg Ser Thr Tyr Ser Ala Pro Arg Thr Gln Trp Arg Pro Gly
                1125                1130                1135

Ser Trp Thr Pro Cys Ser Ala Thr Cys Gly Lys Gly Thr Arg Met Arg
            1140                1145                1150

Tyr Val Ser Cys Arg Asp Glu Asn Gly Ser Val Ala Asp Glu Ser Ala
        1155                1160                1165

Cys Ala Thr Leu Pro Arg Pro Val Ala Lys Glu Glu Cys Ser Val Thr
   1170                1175                1180
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            1220                1225                1230

   Thr Asp Gln Asp Cys Ser Met Ser Pro Cys Pro Gln Arg Thr Pro Asp
          1235                1240                1245

 5
   Ser Gly Leu Ala Gln His Pro Phe Gln Asn Glu Asp Tyr Arg Pro Arg
      1250                1255                1260

   Ser Ala Ser Pro Ser Arg Thr His Val Leu Gly Gly Asn Gln Trp Arg
10 1265                1270                1275                1280

   Thr Gly Pro Trp Gly Ala Cys Ser Ser Thr Cys Ala Gly Gly Ser Gln
                  1285                1290                1295

15 Arg Arg Val Val Val Cys Gln Asp Glu Asn Gly Tyr Thr Ala Asn Asp
              1300                1305                1310

   Cys Val Glu Arg Ile Lys Pro Asp Glu Gln Arg Ala Cys Glu Ser Gly
          1315                1320                1325

20
   Pro Cys Pro Gln Trp Ala Tyr Gly Asn Trp Gly Glu Cys Thr Lys Leu
      1330                1335                1340

   Cys Gly Gly Gly Ile Arg Thr Arg Leu Val Val Ser Gln Arg Ser Asn
25 1345                1350                1355                1360

   Gly Glu Arg Phe Pro Asp Leu Ser Cys Glu Ile Leu Asp Lys Pro Pro
                  1365                1370                1375

30 Asp Arg Glu Gln Cys Asn Thr His Ala Cys Pro His Asp Ala Ala Trp
              1380                1385                1390

   Ser Thr Gly Pro Trp Ser Ser Cys Ser Val Ser Cys Gly Arg Gly His
          1395                1400                1405

35
   Lys Gln Arg Asn Val Tyr Cys Met Ala Lys Asp Gly Ser His Leu Glu
      1410                1415                1420

   Ser Asp Tyr Cys Lys His Leu Ala Lys Pro His Gly His Arg Lys Cys
40 1425                1430                1435                1440

   Arg Gly Gly Arg Cys Pro Lys Trp Lys Ala Gly Ala Trp Ser Gln Cys
                  1445                1450                1455

45 Ser Val Ser Met Gly Arg Gly Val Gln Gln Arg His Val Gly Cys Gln
              1460                1465                1470

   Ile Gly Thr His Lys Ile Ala Arg Glu Thr Glu Cys Asn Pro Tyr Thr
          1475                1480                1485

50
   Arg Pro Glu Ser Glu Cys Glu Cys Gln Gly Pro Arg Cys Pro Leu Tyr
      1490                1495                1500

   Thr Trp Arg Ala Glu Glu Trp Gln Glu Cys Thr Lys Thr Cys Gly Glu
55 1505                1510                1515                1520

   Gly Ser Arg Tyr Arg Lys Val Val Cys Val Asp Asp Asn Lys Asn Glu
                  1525                1530                1535

   Ala Ala Cys Asp Val Thr Lys Arg Pro Pro Leu Ser Gln Arg Leu Val
```

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      1570                1575                1580

   Ser Cys Ser Glu Ile Tyr Thr Gly Lys Glu Asn Tyr Glu Tyr Ser Tyr
   1585                1590                1595                1600
 5
   Gln Thr Thr Ile Asn Cys Pro Gly Thr Gln Pro Pro Ser Val His Pro
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   Cys Tyr Leu Arg Glu Cys Pro Val Ser Ala Thr Trp Arg Val Gly Asn
10            1620                1625                1630

   Trp Gly Ser Cys Ser Val Ser Cys Gly Val Gly Val Met Gln Arg Ser
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15 Val Gln Cys Leu Thr Asn Glu Asp Gln Pro Ser His Leu Cys His Thr
      1650                1655                1660

   Asp Leu Lys Pro Glu Glu Arg Lys Thr Cys Arg Asn Val Tyr Asn Cys
   1665                1670                1675                1680
20
   Glu Leu Pro Gln Asn Cys Lys Glu Val Lys Arg Leu Lys Gly Ala Ser
                   1685                1690                1695

   Glu Asp Gly Glu Tyr Phe Leu Met Ile Arg Gly Lys Leu Leu Lys Ile
25            1700                1705                1710

   Phe Cys Ala Gly Met His Ser Asp His Pro Lys Glu Tyr Val Thr Leu
          1715                1720                1725

30 Val His Gly Asp Ser Glu Asn Phe Ser Glu Val Tyr Gly His Arg Leu
      1730                1735                1740

   His Asn Pro Thr Glu Cys Pro Tyr Asn Gly Ser Arg Arg Asp Asp Cys
   1745                1750                1755                1760
35
   Gln Cys Arg Lys Asp Tyr Thr Ala Ala Gly Phe Ser Ser Phe Gln Lys
                   1765                1770                1775

   Ile Arg Ile Asp Leu Thr Ser Met Gln Ile Ile Thr Thr Asp Leu Gln
40            1780                1785                1790

   Phe Ala Arg Thr Ser Glu Gly His Pro Val Pro Phe Ala Thr Ala Gly
          1795                1800                1805

45 Asp Cys Tyr Ser Ala Ala Lys Cys Pro Gln Gly Arg Phe Ser Ile Asn
      1810                1815                1820

   Leu Tyr Gly Thr Gly Leu Ser Leu Thr Glu Ser Ala Arg Trp Ile Ser
   1825                1830                1835                1840
50
   Gln Gly Asn Tyr Ala Val Ser Asp Ile Lys Lys Ser Pro Asp Gly Thr
                   1845                1850                1855

   Arg Val Val Gly Lys Cys Gly Gly Tyr Cys Gly Lys Cys Thr Pro Ser
55            1860                1865                1870

   Ser Gly Thr Gly Leu Glu Val Arg Val Leu
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tct cac gat gga gat tat ttc att gaa cca ctg cag tct gtg gat gag 97
Ser His Asp Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Val Asp Glu
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Gln Glu Asp Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg His
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Ser Thr Pro Gln Arg Glu Pro Ser Thr Gly Lys His Ala Cys Ala Thr
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Ser Glu Leu Lys Asn Ser His Ser Lys Asp Lys Arg Lys Ile Arg Met
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cga aaa cgg aga aag agg aat agc ctg gct gac gac gtg gca ctg cta 289
Arg Lys Arg Arg Lys Arg Asn Ser Leu Ala Asp Asp Val Ala Leu Leu
85 90 95

aag agc ggt ttg gca aca aag gtg ctc tct ggc tat agc aac cag aca 337
Lys Ser Gly Leu Ala Thr Lys Val Leu Ser Gly Tyr Ser Asn Gln Thr
100 105 110

aac aac aca agg gac aga tgg aac cac aaa aga acc aaa cgc ttt ctg 385
Asn Asn Thr Arg Asp Arg Trp Asn His Lys Arg Thr Lys Arg Phe Leu
115 120 125

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Ser Tyr Pro Arg Phe Val Glu Val Met Val Val Ala Asp His Arg Met
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Val Leu Tyr His Gly Ala Asn Leu Gln His Tyr Ile Leu Thr Leu Met
145 150 155 160

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Ser Ile Val Ala Ser Ile Tyr Lys Asp Ser Ser Ile Gly Asn Leu Ile
165 170 175

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Asn Ile Val Ile Val Asn Leu Val Val Ile His Asn Glu Gln Glu Gly
180 185 190

cct tac ata aat ttc aat gcc cag aca aca tta aag aac ttt tgc cag 625
Pro Tyr Ile Asn Phe Asn Ala Gln Thr Thr Leu Lys Asn Phe Cys Gln
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   His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ser Asn Lys
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   tgc aaa gaa gaa gga gtt aag agt ccc cag cat gtc atg gca cca aca   913
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   ctg aac ttc tac acc aac ccc tgg atg tgg tca aag tgc agt cgg aaa   961
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   Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn
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   gaa cct gca tcc agg acc tat cct ttg cct tcc caa ctg ccc ggc ctt  1057
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               340                 345                 350

   ctc tac aac gtg aat aaa caa tgt gaa ctg att ttt ggg cca ggc tct  1105
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   caa gtg tgc ccc tat atg atg cag tgc aga cgg ctc tgg tgc aat aat  1153
   Gln Val Cys Pro Tyr Met Met Gln Cys Arg Arg Leu Trp Cys Asn Asn
       370                 375                 380
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   gtg gat gga gca cac aaa ggc tgc aag act cag cac acg ccc tgg gca  1201
   Val Asp Gly Ala His Lys Gly Cys Lys Thr Gln His Thr Pro Trp Ala
   385                 390                 395                 400

40 gat gga acc gag tgt gag cct gga aag cac tgc aag ttt gga ttt tgt  1249
   Asp Gly Thr Glu Cys Glu Pro Gly Lys His Cys Lys Phe Gly Phe Cys
                   405                 410                 415

   gtt ccc aaa gaa atg gag ggc cct gca att gat gga tcc tgg gga ggt  1297
45 Val Pro Lys Glu Met Glu Gly Pro Ala Ile Asp Gly Ser Trp Gly Gly
               420                 425                 430

   tgg agc cac ttt ggg acc tgc tca aga acg tgt gga gga ggc att aaa  1345
   Trp Ser His Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile Lys
50         435                 440                 445

   aca ggc atc aga gag tgc aac aga cca gag cca aaa aat ggt ggg aag  1393
   Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly Lys
       450                 455                 460
55
   tac tgt gta gga agg aga atg aag ttc aaa tcc tgc aac acg gag ccc  1441
   Tyr Cys Val Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu Pro
   465                 470                 475                 480

   Asp Lys Lys His Pro Leu Ile Asn Gly Val Arg Trp
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```

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   ttt cct aag tac agc gga att ttg atg aag gac cgg tgc aag ttg ttc   1585
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           515                 520                 525
5
   tgc aga gtg gca gga aac aca gcc tac tac cag ctc cga gac aga gtg   1633
   Cys Arg Val Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg Val
       530                 535                 540

10 att gac gga acc cct tgt ggc cag gac aca aat gac atc tgt gtc caa   1681
   Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val Gln
   545                 550                 555                 560

   ggc ctt tgc cgg caa gct gga tgt gat cat att tta aac tca aag gtc   1729
15 Gly Leu Cys Arg Gln Ala Gly Cys Asp His Ile Leu Asn Ser Lys Val
                   565                 570                 575

   cgg aaa gat aaa tgt ggg att tgt ggt gga gat aat tct tca tgc aaa   1777
   Arg Lys Asp Lys Cys Gly Ile Cys Gly Gly Asp Asn Ser Ser Cys Lys
20             580                 585                 590

   aca gtg gca gga aca ttt aac act gtc cat tat ggt tac aat act gtt   1825
   Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr Val
           595                 600                 605
25
   gtc cga att ccg gct ggt gct acc agc att gac gtg cgt cag cac agc   1873
   Val Arg Ile Pro Ala Gly Ala Thr Ser Ile Asp Val Arg Gln His Ser
       610                 615                 620

30 ttc tca ggg aag tct gag gat gac aac tac cta gct tta tca aac agt   1921
   Phe Ser Gly Lys Ser Glu Asp Asp Asn Tyr Leu Ala Leu Ser Asn Ser
   625                 630                 635                 640

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35 Lys Gly Glu Phe Leu Leu Asn Gly Asp Phe Val Val Ser Met Ser Lys
                   645                 650                 655

   agg gag gtc cgc gtg ggg agc gcc gtc att gag tac agc gga tcg gac   2017
   Arg Glu Val Arg Val Gly Ser Ala Val Ile Glu Tyr Ser Gly Ser Asp
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           675                 680                 685
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   ttg ctt cag gtg ttg tcc gtg gga aag ctg tat aac cca gat gtg cgg   2113
   Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val Arg
       690                 695                 700

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   Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr Trp
   705                 710                 715                 720

   aac agt cac ggg ccg tgg caa gca tgc agc aag ccc tgc caa ggg gag   2209
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                   725                 730                 735

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       770                 775                 780

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 5 Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile His
   785                 790                 795                 800

   tgt gcc aaa tac agc agg atg gac ggg aag acg gag aag gtg gat gac   2449
   Cys Ala Lys Tyr Ser Arg Met Asp Gly Lys Thr Glu Lys Val Asp Asp
10                 805                 810                 815

   agt ttc tgt agc agt caa ccc aga ccg agt aac cag gag aaa tgc tca   2497
   Ser Phe Cys Ser Ser Gln Pro Arg Pro Ser Asn Gln Glu Lys Cys Ser
               820                 825                 830
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   gga gag tgc agc aca ggt gga tgg cgc tat tca gcc tgg acc gaa tgt   2545
   Gly Glu Cys Ser Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu Cys
           835                 840                 845

20 tct aga agc tgt gat ggt ggt acc cac aga aga aga gca att tgt gtc   2593
   Ser Arg Ser Cys Asp Gly Gly Thr His Arg Arg Arg Ala Ile Cys Val
       850                 855                 860

   aac acc cgc aat gat gtc ctg gat gac agc aa                       2625
25 Asn Thr Arg Asn Asp Val Leu Asp Asp Ser
   865                 870


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   Ser His Asp Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Val Asp Glu
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40
   Gln Glu Asp Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg His
           35                  40                  45

   Ser Thr Pro Gln Arg Glu Pro Ser Thr Gly Lys His Ala Cys Ala Thr
45     50                  55                  60

   Ser Glu Leu Lys Asn Ser His Ser Lys Asp Lys Arg Lys Ile Arg Met
   65                  70                  75                  80

50 Arg Lys Arg Arg Lys Arg Asn Ser Leu Ala Asp Arg Val Ala Leu Leu
                   85                  90                  95

   Lys Ser Gly Leu Ala Thr Lys Val Leu Ser Gly Tyr Ser Asn Gln Thr
               100                 105                 110
55
   Asn Asn Thr Arg Asp Arg Trp Asn His Lys Arg Thr Lys Arg Phe Leu
           115                 120                 125

   Thr Ile Val Ala Arg Ile Tyr Lys Arg Ile Ile Asn Leu Val Asn
       130                 135                 140
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Asn Ile Val Ile Val Asn Leu Val Val Ile His Asn Glu Gln Glu Gly
180 185 190

Pro Tyr Ile Asn Phe Asn Ala Gln Thr Thr Leu Lys Asn Phe Cys Gln
195 200 205

Trp Gln His Ser Lys Asn Tyr Leu Gly Gly Ile Gln His Asp Thr Ala
210 215 220

Val Leu Val Thr Arg Glu Asp Ile Cys Arg Ala Gln Asp Lys Cys Asp
225 230 235 240

Thr Leu Gly Leu Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg Ser
245 250 255

Cys Ser Ile Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile Ala
260 265 270

His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ser Asn Lys
275 280 285

Cys Lys Glu Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro Thr
290 295 300

Leu Asn Phe Tyr Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg Lys
305 310 315 320

Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn
325 330 335

Glu Pro Ala Ser Arg Thr Tyr Pro Leu Pro Ser Gln Leu Pro Gly Leu
340 345 350

Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly Ser
355 360 365

Gln Val Cys Pro Tyr Met Met Gln Cys Arg Arg Leu Trp Cys Asn Asn
370 375 380

Val Asp Gly Ala His Lys Gly Cys Lys Thr Gln His Thr Pro Trp Ala
385 390 395 400

Asp Gly Thr Glu Cys Glu Pro Gly Lys His Cys Lys Phe Gly Phe Cys
405 410 415

Val Pro Lys Glu Met Glu Gly Pro Ala Ile Asp Gly Ser Trp Gly Gly
420 425 430

Trp Ser His Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile Lys
435 440 445

Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly Lys
450 455 460

Tyr Cys Val Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu Pro
465 470 475 480

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Cys Arg Val Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg Val
530                 535                 540

Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val Gln
545                 550                 555                 560

Gly Leu Cys Arg Gln Ala Gly Cys Asp His Ile Leu Asn Ser Lys Val
                565                 570                 575

Arg Lys Asp Lys Cys Gly Ile Cys Gly Gly Asp Asn Ser Ser Cys Lys
            580                 585                 590

Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr Val
        595                 600                 605

Val Arg Ile Pro Ala Gly Ala Thr Ser Ile Asp Val Arg Gln His Ser
    610                 615                 620

Phe Ser Gly Lys Ser Glu Asp Asp Asn Tyr Leu Ala Leu Ser Asn Ser
625                 630                 635                 640

Lys Gly Glu Phe Leu Leu Asn Gly Asp Phe Val Val Ser Met Ser Lys
                645                 650                 655

Arg Glu Val Arg Val Gly Ser Ala Val Ile Glu Tyr Ser Gly Ser Asp
            660                 665                 670

Asn Val Cys Glu Arg Leu Asn Cys Thr Asp Arg Ile Glu Glu Glu Leu
        675                 680                 685

Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val Arg
    690                 695                 700

Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr Trp
705                 710                 715                 720

Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly Glu
                725                 730                 735

Arg Arg Pro Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr Val
            740                 745                 750

Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly Pro Val Thr Glu
        755                 760                 765

Ala Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Lys Ser
    770                 775                 780

Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile His
785                 790                 795                 800

Cys Ala Lys Tyr Ser Arg Met Asp Gly Lys Thr Glu Lys Val Asp Asp
                805                 810                 815

Ser Phe Cys Ser Ser Gln Pro Arg Pro Ser Asn Gln Glu Lys Cys Ser
            820                 825                 830

Asn Thr Ala Asn Asp Leu Leu Asp Arg Val
        835                 840
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Ser Arg Thr Pro Ser Gly Leu Lys Met Ser Ser Cys Pro Val Trp Arg
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gct atg aga tcg cct tcc tca ccc gcg tgg acc aca acg ggg cac tgc 96
Ala Met Arg Ser Pro Ser Pro Pro Ala Trp Thr Thr Thr Gly His Cys
20 25 30

tgg cct tct cgc cac ctc ctc ccc gga gca gcg ccg cgg cac ggg ggc 144
Trp Pro Ser Arg His Leu Leu Pro Gly Ala Ala Pro Arg His Gly Gly
35 40 45

cac agc cga gtc ccg cct ctt cta caa agt ggc ctc gcc agc acc cac 192
His Ser Arg Val Pro Pro Leu Leu Gln Ser Gly Leu Ala Ser Thr His
50 55 60

ttc ctg ctg aac ctg acc cgc agc tcc cgt cta ctg gca ggg cgc gtc 240
Phe Leu Leu Asn Leu Thr Arg Ser Ser Arg Leu Leu Ala Gly Arg Val
65 70 75 80

tcc gtg gag tac tgg aca cgg gag ggc ctg gcc tgg cag agg gcg gcc 288
Ser Val Glu Tyr Trp Thr Arg Glu Gly Leu Ala Trp Gln Arg Ala Ala
85 90 95

cgg ccc cac tgc ctc tac gct ggt cac ctg cag ggc cag gcc agc agc 336
Arg Pro His Cys Leu Tyr Ala Gly His Leu Gln Gly Gln Ala Ser Ser
100 105 110

tcc cat gtg gcc atc agc acc tgt gga ggc ctg cac ggc ctg atc gtg 384
Ser His Val Ala Ile Ser Thr Cys Gly Gly Leu His Gly Leu Ile Val
115 120 125

gca gac gag gaa gag tac ctg att gag ccc ctg cac ggt ggg ccc aag 432
Ala Asp Glu Glu Glu Tyr Leu Ile Glu Pro Leu His Gly Gly Pro Lys
130 135 140

ggt tct cgg agt ccg gag gaa agt gga ccg cat tgt gtg tac aag cgt 480
Gly Ser Arg Ser Pro Glu Glu Ser Gly Pro His Cys Val Tyr Lys Arg
145 150 155 160

tcc tcc ctg cgt cac ccc cac ctg gac aca gcc tgt gga gtg aga gat 528
Ser Ser Leu Arg His Pro His Leu Asp Thr Ala Cys Gly Val Arg Asp
165 170 175

[illegible] 576

[illegible] 672

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   Leu Lys Arg Ser Val Ser Arg Glu Arg Tyr Val Glu Thr Met Asp Val
       210                 215                 220

   gct gac aag atg atg gtg gcc tat cac ggg cgc cgg gat gtg gag cag   720
 5 Ala Asp Lys Met Met Val Ala Tyr His Gly Arg Arg Asp Val Glu Gln
   225                 230                 235                 240

   tat gtc ctg gcc atc atg aac att gtt gcc aaa ctt ttc cag gac tcg   768
   Tyr Val Leu Ala Ile Met Asn Ile Val Ala Lys Leu Phe Gln Asp Ser
10                 245                 250                 255

   agt ctg gga agc acc gtt aac atc ctc gta act cgc ctc atc ctg ctc   816
   Ser Leu Gly Ser Thr Val Asn Ile Leu Val Thr Arg Leu Ile Leu Leu
               260                 265                 270
15
   acg gag gac cag ccc act ctg gag atc acc cac cat gcc ggg aag tcc   864
   Thr Glu Asp Gln Pro Thr Leu Glu Ile Thr His His Ala Gly Lys Ser
           275                 280                 285

20 cta gac agc ttc tgt aag tgg cag aaa tcc atc gtg aac cac agc ggc   912
   Leu Asp Ser Phe Cys Lys Trp Gln Lys Ser Ile Val Asn His Ser Gly
       290                 295                 300

   cat ggc aat gcc att cca gag aac ggt gtg gct aac cat gac aca gca   960
25 His Gly Asn Ala Ile Pro Glu Asn Gly Val Ala Asn His Asp Thr Ala
   305                 310                 315                 320

   gtg ctc atc aca cgc tat gac atc tgc atc tac aag aac aaa ccc tgc  1008
   Val Leu Ile Thr Arg Tyr Asp Ile Cys Ile Tyr Lys Asn Lys Pro Cys
30                 325                 330                 335

   ggc aca cta ggc ctg gcc cgg tgg gcg gaa tgt gtg agc gcg aga gaa  1056
   Gly Thr Leu Gly Leu Ala Arg Trp Ala Glu Cys Val Ser Ala Arg Glu
               340                 345                 350
35
   gct gca gcg tca atg agg aca ttg gct gcc aca agc gtt cac cat tgc  1104
   Ala Ala Ala Ser Met Arg Thr Leu Ala Ala Thr Ser Val His His Cys
           355                 360                 365

40 cac gag atc ggg cac aca ttc ggc atg aac cat gac ggc gtg gga aac  1152
   His Glu Ile Gly His Thr Phe Gly Met Asn His Asp Gly Val Gly Asn
       370                 375                 380

   agc tgt ggg gcc cgt ggt cag gac cca gcc aag ctc atg gct gcc cac  1200
45 Ser Cys Gly Ala Arg Gly Gln Asp Pro Ala Lys Leu Met Ala Ala His
   385                 390                 395                 400

   att acc atg aag acc aac cca ttc gtg tgg tca tcc tgc aac ggt gac  1248
   Ile Thr Met Lys Thr Asn Pro Phe Val Trp Ser Ser Cys Asn Arg Asp
50                 405                 410                 415

   tac atc acc agc ttt cta gac tcg ggc ctg ggg ctc tgc ctg aac aac  1296
   Tyr Ile Thr Ser Phe Leu Asp Ser Gly Leu Gly Leu Cys Leu Asn Asn
               420                 425                 430
55
   ggg ccc ccc aga cag gac ttt gtg tac ccg acg gtg gca ccg ggc caa  1344
   Arg Pro Pro Arg Gln Asp Phe Val Tyr Pro Thr Val Ala Pro Gly Gln
           435                 440                 445

   [illegible]                                                     1392
   [illegible]
   450                 455                 460
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   aag agc aac cgg tgc atc acc aac agc atc ccg gcc gcc gag ggc acg   1488
   Lys Ser Asn Arg Cys Ile Thr Asn Ser Ile Pro Ala Ala Glu Gly Thr
                   485                 490                 495
5
   ctg tgc cag acg cac acc atc gac aag ggg tgg tgc tac aaa cgg gtc   1536
   Leu Cys Gln Thr His Thr Ile Asp Lys Gly Trp Cys Tyr Lys Arg Val
               500                 505                 510

10 tgt gtc ccc ttt ggg tcg cgc cca gag ggt gtg gac gga gcc tgg ggg   1584
   Cys Val Pro Phe Gly Ser Arg Pro Glu Gly Val Asp Gly Ala Trp Gly
           515                 520                 525

   ccg tgg act cca tgg ggc gac tgc agc cgg acc tgt ggc ggc ggc gtg   1632
15 Pro Trp Thr Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly Gly Val
       530                 535                 540

   tcc tct tct agt cgt cac tgc gac agc ccc agg cca acc atc ggg ggc   1680
   Ser Ser Ser Ser Arg His Cys Asp Ser Pro Arg Pro Thr Ile Gly Gly
20 545                 550                 555                 560

   aag tac tgt ctg ggt gag aga agg cgg cac cgc tcc tgc aac acg gat   1728
   Lys Tyr Cys Leu Gly Glu Arg Arg Arg His Arg Ser Cys Asn Thr Asp
                   565                 570                 575
25
   gac tgt ccc cct ggc tcc cag gac ttc aga gaa gtg cag tgt gct gaa   1776
   Asp Cys Pro Pro Gly Ser Gln Asp Phe Arg Glu Val Gln Cys Ala Glu
               580                 585                 590

30 ttt gac agc atc cct ttc cgt ggg aaa ttc tac aag tgg aaa acg tac   1824
   Phe Asp Ser Ile Pro Phe Arg Gly Lys Phe Tyr Lys Trp Lys Thr Tyr
           595                 600                 605

   cgg gga ggg ggc gtg aag gcc tgc tcg ctc acg agc cta gtg gaa ggc   1872
35 Arg Gly Gly Gly Val Lys Ala Cys Ser Leu Thr Ser Leu Ala Glu Gly
       610                 615                 620

   ttc aac ttc tac acg gag agg gcg gca gcc gtg gtg gac ggg aca ccc   1920
   Phe Asn Phe Tyr Thr Glu Arg Ala Ala Ala Val Val Asp Gly Thr Pro
40 625                 630                 635                 640

   tgc cgt cca gac acg gtg gac att tgc gtc agt ggc gaa tgc aag cac   1968
   Cys Arg Pro Asp Thr Val Asp Ile Cys Val Ser Gly Glu Cys Lys His
                   645                 650                 655
45
   gtg ggg tgc gac cga gtc ctg ggc tcc gac ctg cgg gag gac aag tgc   2016
   Val Gly Cys Asp Arg Val Leu Gly Ser Asp Leu Arg Glu Asp Lys Cys
               660                 665                 670

   agg gtg tgt ggg ggt gac ggg agt gcc tgc gag acc atc agg ggc gtc   2064
   Arg Val Cys Gly Gly Asp Gly Ser Ala Cys Glu Thr Ile Arg Gly Val
           675                 680                 685

   ttc agc cca gcc tca cct ggg gcc ggg tac gag gat gtc gtc tgg att   2112
55 Phe Ser Pro Ala Ser Pro Gly Ala Gly Tyr Glu Asp Val Val Trp Ile
       690                 695                 700

   ccc aaa ggc tcc gtg gac atg ttt atc cag gat ctg aac gtc tct gtc   2160
```

```
   ctg tct ggt acc ccc tcc tcc ctc tcc tgt gtg ctc cta gct ggg ttt
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   Leu Pro Gly Thr Pro Gln Pro His Arg Leu Pro Leu Ala Gly Thr Thr
                740                 745                 750

   ttt caa ctg cga cag ggg cca gac cag gtc cag agc ctc gaa gcc ctg   2304
 5 Phe Gln Leu Arg Gln Gly Pro Asp Gln Val Gln Ser Leu Glu Ala Leu
          755                 760                 765

   gga ccg att aat gca tct ctc atc gtc atg gtg ctg gcc cgg acc gag   2352
   Gly Pro Ile Asn Ala Ser Leu Ile Val Met Val Leu Ala Arg Thr Glu
10      770                 775                 780

   ctg cct gcc ctc cgc tac cgc ttc aat gcc ccc atc gcc cgt gac tcg   2400
   Leu Pro Ala Leu Arg Tyr Arg Phe Asn Ala Pro Ile Ala Arg Asp Ser
   785                 790                 795                 800
15
   ctg ccc ccc tac tcc tgg cac tat gcg ccc tgg acc aag tgc tcg gcc   2448
   Leu Pro Pro Tyr Ser Trp His Tyr Ala Pro Trp Thr Lys Cys Ser Ala
                805                 810                 815

20 cag tgt gca ggc ggt agt cag gtg cag gcg gtg gag tgc cgc aac cag   2496
   Gln Cys Ala Gly Gly Ser Gln Val Gln Ala Val Glu Cys Arg Asn Gln
                820                 825                 830

   ctg gac agc tcc gcg gtt gcc ccc cac tat tgc agt gcc cac agc aag   2544
25 Leu Asp Ser Ser Ala Val Ala Pro His Tyr Cys Ser Ala His Ser Lys
          835                 840                 845

   ctg ccc aaa agg cag cgt gcc tgc aac acg gag cct tgc cct cca gac   2592
   Leu Pro Lys Arg Gln Arg Ala Cys Asn Thr Glu Pro Cys Pro Pro Asp
30      850                 855                 860

   tgg gtt gta ggg aac tgg tcg ctc tgc agt cgc agc tgc gat gca ggc   2640
   Trp Val Val Gly Asn Trp Ser Leu Cys Ser Arg Ser Cys Asp Ala Gly
   865                 870                 875                 880
35
   gtg cgc agt acg tcg gtt gtg tgc cag cgt cgc gtc tct gcc gcg gag   2688
   Val Arg Ser Thr Ser Val Val Cys Gln Arg Arg Val Ser Ala Ala Glu
                885                 890                 895

40 gag aag gcg ctg gac gac agc gca tgc ccg cag ccg cgc cca cct gta   2736
   Glu Lys Ala Leu Asp Asp Ser Ala Cys Pro Gln Pro Arg Pro Pro Val
                900                 905                 910

   ctg gag gcc tgc cac ggt ccc act tgc cct ccg gag tgg gca acc ctc   2784
45 Leu Glu Ala Cys His Gly Pro Thr Cys Pro Pro Glu Trp Ala Thr Leu
          915                 920                 925

   gac tgg tct gag tgt acc cca agc tgt ggg cct ggt ctc cgc cac cga   2832
   Asp Trp Ser Glu Cys Thr Pro Ser Cys Gly Pro Gly Leu Arg His Arg
50      930                 935                 940

   gtg gtc ctt tgt aag agt gca gat caa cga tct act ctg ccc cct ggg   2880
   Val Val Leu Cys Lys Ser Ala Asp Gln Arg Ser Thr Leu Pro Pro Gly
   945                 950                 955                 960
55
   cac tgc ctt cct gca gcc aag cca cca tct act atg cga tgt aac ttg   2928
   His Cys Leu Pro Ala Ala Lys Pro Pro Ser Thr Met Arg Cys Asn Leu
                965                 970                 975

   ctt gaa tgg tct gat gtg gag ctc agt gac ttt ctc aag aac aag tct   3024
   Leu Glu Trp Ser Asp Val Glu Leu Ser Asp Phe Leu Lys Asn Lys Ser
          995                1000                1005
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   agc cac acc ggc cag cca tct cga gag tgc act gaa gcc ttg cgg cca   3072
   Ser His Thr Gly Gln Pro Ser Arg Glu Cys Thr Glu Ala Leu Arg Pro
      1010                1015                1020
5
   tcc acc atg cag cag tgt gag gcc aag tgt gac agt gtg gtg ccg cct   3120
   Ser Thr Met Gln Gln Cys Glu Ala Lys Cys Asp Ser Val Val Pro Pro
   1025               1030                1035                1040

10 gga gat ggc cca gaa gaa tgc aag gat gtg aac aag gtg gct tac tgc   3168
   Gly Asp Gly Pro Glu Glu Cys Lys Asp Val Asn Lys Val Ala Tyr Cys
                  1045                1050                1055

   ccc ctg gtg ctc aaa ttt cag ttc tgt agc cga gcc tac ttc cgc cag   3216
15 Pro Leu Val Leu Lys Phe Gln Phe Cys Ser Arg Ala Tyr Phe Arg Gln
              1060                1065                1070

   atg tgc tgc aaa acc tgc caa ggc cgc tag ggtacctgga accaacctgg     3266
   Met Cys Cys Lys Thr Cys Gln Gly Arg
20        1075                1080

   agtacaggct gaggcagggg acatcccact ggagagggca tgagggaaag gggggcttga 3326

   attgaagggt gagatgcagt tgaaagttat ttattgggta accctacagg gctcctgact 3386
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   aaggggtgga gaagagctgg ctacccaggg accctctgct gtatcttgcc cagttgatag 3446

   tgaagagaga ggactccttg ttgcacacat atttaagtcc ctagcacccc tcccaccctt 3506

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   ttgcactgtt ctatccctac actctgagct gggggggattt atatctgcta tgggggcagt 3626

   aggcttgata ccacctccct gtagccctcc cccagactga cgaaggggaa gatccacccc 3686
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   aacctctgcc ctgcctgccc caggggggag ttcaacatcc aggccgttcc ccatcatggt 3746

   gctacaagcc ctgccctggg gcccacacac tcctcaccaa gaagccttac attaaaaaag 3806

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   tatagtaaat ngggtnttta                                             3885


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   <213> Homo sapiens ALAMTS 11

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   Ala Met Arg Ser Pro Ser Pro Pro Ala Trp Thr Thr Thr Gly His Cys
                20                  25                  30
55 Trp Pro Ser Arg His Leu Leu Pro Gly Ala Ala Pro Arg His Gly Gly
            35                  40                  45
   His Ser Arg Val Pro Pro Leu Leu Gln Ser Gly Leu Ala Ser Thr His
        50                  55                  60

65 Pro Ala Ala Ile Pro Thr Leu Ile Asp Trp Ile Asp Val Glu Phe Val
   65                  70                  75                  80
            115                 120                 125
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```
Ala Asp Glu Glu Glu Tyr Leu Ile Glu Pro Leu His Gly Gly Pro Lys
    130                 135                 140
Gly Ser Arg Ser Pro Glu Glu Ser Gly Pro His Cys Val Tyr Lys Arg
145                 150                 155                 160
Ser Ser Leu Arg His Pro His Leu Asp Thr Ala Cys Gly Val Arg Asp
                165                 170                 175
Glu Lys Pro Trp Lys Gly Arg Pro Trp Trp Leu Arg Thr Leu Lys Pro
            180                 185                 190
Pro Pro Ala Arg Pro Leu Gly Asn Glu Thr Glu Arg Gly Gln Pro Gly
        195                 200                 205
Leu Lys Arg Ser Val Ser Arg Glu Arg Tyr Val Glu Thr Met Asp Val
    210                 215                 220
Ala Asp Lys Met Met Val Ala Tyr His Gly Arg Arg Asp Val Glu Gln
225                 230                 235                 240
Tyr Val Leu Ala Ile Met Asn Ile Val Ala Lys Leu Phe Gln Asp Ser
                245                 250                 255
Ser Leu Gly Ser Thr Val Asn Ile Leu Val Thr Arg Leu Ile Leu Leu
            260                 265                 270
Thr Glu Asp Gln Pro Thr Leu Glu Ile Thr His His Ala Gly Lys Ser
        275                 280                 285
Leu Asp Ser Phe Cys Lys Trp Gln Lys Ser Ile Val Asn His Ser Gly
    290                 295                 300
His Gly Asn Ala Ile Pro Glu Asn Gly Val Ala Asn His Asp Thr Ala
305                 310                 315                 320
Val Leu Ile Thr Arg Tyr Asp Ile Cys Ile Tyr Lys Asn Lys Pro Cys
                325                 330                 335
Gly Thr Leu Gly Leu Ala Arg Trp Ala Glu Cys Val Ser Ala Arg Glu
            340                 345                 350
Ala Ala Ala Ser Met Arg Thr Leu Ala Ala Thr Ser Val His His Cys
        355                 360                 365
His Glu Ile Gly His Thr Phe Gly Met Asn His Asp Gly Val Gly Asn
    370                 375                 380
Ser Cys Gly Ala Arg Gly Gln Asp Pro Ala Lys Leu Met Ala Ala His
385                 390                 395                 400
Ile Thr Met Lys Thr Asn Pro Phe Val Trp Ser Ser Cys Asn Arg Asp
                405                 410                 415
Tyr Ile Thr Ser Phe Leu Asp Ser Gly Leu Gly Leu Cys Leu Asn Asn
            420                 425                 430
Arg Pro Pro Arg Gln Asp Phe Val Tyr Pro Thr Val Ala Pro Gly Gln
        435                 440                 445
Ala Tyr Asp Ala Asp Glu Gln Cys Arg Phe Gln His Gly Val Lys Ser
    450                 455                 460
Arg Gln Cys Lys Tyr Gly Glu Val Cys Ser Glu Leu Trp Cys Leu Ser
465                 470                 475                 480
Lys Ser Asn Arg Cys Ile Thr Asn Ser Ile Pro Ala Ala Glu Gly Thr
                485                 490                 495
Leu Cys Gln Thr His Thr Ile Asp Lys Gly Trp Cys Tyr Lys Arg Val
            500                 505                 510
Cys Val Pro Phe Gly Ser Arg Pro Glu Gly Val Asp Gly Ala Trp Gly
        515                 520                 525
Pro Trp Thr Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly Gly Val
    530                 535                 540
Ser Ser Ser Ser Arg His Cys Asp Ser Pro Arg Pro Thr Ile Gly Gly
545                 550                 555                 560
Lys Tyr Cys Leu Gly Glu Arg Arg Arg His Arg Ser Cys Asn Thr Asp
                565                 570                 575
Asp Cys Pro Pro Gly Ser Gln Asp Phe Arg Glu Val Gln Cys Ala Glu
            580                 585                 590
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Cys Asp Ser Asp Ile Val Asp Leu Lys Val Met Gly Leu Cys Leu Ser
            595                 600                 605
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Val Gly Cys Asp Arg Val Leu Gly Ser Asp Leu Arg Glu Asp Lys Cys
            660                 665                 670
Arg Val Cys Gly Gly Asp Gly Ser Ala Cys Glu Thr Ile Glu Gly Val
        675                 680                 685
Phe Ser Pro Ala Ser Pro Gly Ala Gly Tyr Glu Asp Val Val Trp Ile
    690                 695                 700
Pro Lys Gly Ser Val His Ile Phe Ile Gln Asp Leu Asn Leu Ser Leu
705                 710                 715                 720
Ser His Leu Ala Leu Lys Gly Asp Gln Glu Ser Leu Leu Leu Glu Gly
                725                 730                 735
Leu Pro Gly Thr Pro Gln Pro His Arg Leu Pro Leu Ala Gly Thr Thr
            740                 745                 750
Phe Gln Leu Arg Gln Gly Pro Asp Gln Val Gln Ser Leu Glu Ala Leu
        755                 760                 765
Gly Pro Ile Asn Ala Ser Leu Ile Val Met Val Leu Ala Arg Thr Glu
    770                 775                 780
Leu Pro Ala Leu Arg Tyr Arg Phe Asn Ala Pro Ile Ala Arg Asp Ser
785                 790                 795                 800
Leu Pro Pro Tyr Ser Trp His Tyr Ala Pro Trp Thr Lys Cys Ser Ala
                805                 810                 815
Gln Cys Ala Gly Gly Ser Gln Val Gln Ala Val Glu Cys Arg Asn Gln
            820                 825                 830
Leu Asp Ser Ser Ala Val Ala Pro His Tyr Cys Ser Ala His Ser Lys
        835                 840                 845
Leu Pro Lys Arg Gln Arg Ala Cys Asn Thr Glu Pro Cys Pro Pro Asp
    850                 855                 860
Trp Val Val Gly Asn Trp Ser Leu Cys Ser Arg Ser Cys Asp Ala Gly
865                 870                 875                 880
Val Arg Ser Thr Ser Val Val Cys Gln Arg Arg Val Ser Ala Ala Glu
                885                 890                 895
Glu Lys Ala Leu Asp Asp Ser Ala Cys Pro Gln Pro Arg Pro Pro Val
            900                 905                 910
Leu Glu Ala Cys His Gly Pro Thr Cys Pro Pro Glu Trp Ala Thr Leu
        915                 920                 925
Asp Trp Ser Glu Cys Thr Pro Ser Cys Gly Pro Gly Leu Arg His Arg
    930                 935                 940
Val Val Leu Cys Lys Ser Ala Asp Gln Arg Ser Thr Leu Pro Pro Gly
945                 950                 955                 960
His Cys Leu Pro Ala Ala Lys Pro Pro Ser Thr Met Arg Cys Asn Leu
                965                 970                 975
Arg Arg Cys Pro Pro Ala Arg Trp Val Thr Ser Glu Trp Gly Glu Cys
            980                 985                 990
Ser Thr Gln Cys Gly Leu Gly Gln Gln Gln Arg Thr Val Arg Cys Thr
        995                1000                1005
Ser His Thr Gly Gln Pro Ser Arg Glu Cys Thr Glu Ala Leu Arg Pro
    1010                1015                1020
Ser Thr Met Gln Gln Cys Glu Ala Lys Cys Asp Ser Val Val Pro Pro
1025                1030                1035                1040
Gly Asp Gly Pro Glu Glu Cys Lys Asp Val Asn Lys Val Ala Tyr Cys
                1045                1050                1055
Pro Leu Val Leu Lys Phe Gln Phe Cys Ser Arg Ala Tyr Phe Arg Gln
            1060                1065                1070
Met Cys Cys Lys Thr Cys Gln Gly Arg
        1075                1080
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<222> (338)..(340)

<220>
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<222> (353)..(355)

<400> 18

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  Ala Ala Ala Val Val Asp Gly Thr Pro Cys Arg Pro Asp Thr Val Asp
    1               5                  10                  15

att tgt gtc agc ggc gag tgc aag cat gta ggc tgt gac agg ctc ctg   97
Ile Cys Val Ser Gly Glu Cys Lys His Val Gly Cys Asp Arg Leu Leu
            20                  25                  30

ggt tct gat ctc cga gag gac aaa tgc cgt gtg tgt ggg ggt gat ggc   145
Gly Ser Asp Leu Arg Glu Asp Lys Cys Arg Val Cys Gly Gly Asp Gly
        35                  40                  45

agt gcc tgt gag acc att gaa ggt gtc ttt agc cca gct ttg cca gga   193
Ser Ala Cys Glu Thr Ile Glu Gly Val Phe Ser Pro Ala Leu Pro Gly
    50                  55                  60

act ggg tat gag gac gtc gtc tgg atc ccc aaa ggc tcg gtc cac att   241
Thr Gly Tyr Glu Asp Val Val Trp Ile Pro Lys Gly Ser Val His Ile
65                  70                  75                  80

ttc atc caa gat ctg aac ctg tcc ctg agt cac ctg gcc cta aag ggg   289
Phe Ile Gln Asp Leu Asn Leu Ser Leu Ser His Leu Ala Leu Lys Gly
                85                  90                  95

gac caa gag tct ctg cta ctg gag ggg cta cct ggg acc ccc caa cct   337
Asp Gln Glu Ser Leu Leu Leu Glu Gly Leu Pro Gly Thr Pro Gln Pro
            100                 105                 110

nac cgc ctt ccc ctg gnt ggg acc aca ttt cat cta cgg cag ggg ccg   385
Xaa Arg Leu Pro Leu Xaa Gly Thr Thr Phe His Leu Arg Gln Gly Pro
        115                 120                 125

gac cag gca cag agc ctg gaa gcc ctg gga ccc att aat gca tct ctc   433
Asp Gln Ala Gln Ser Leu Glu Ala Leu Gly Pro Ile Asn Ala Ser Leu
    130                 135                 140

ttc atc atg gtg ctg ggc cag gca gag ttg cct gct ctc cac tac cgc   481
Ile Ile Met Val Leu Ala Gln Ala Glu Leu Pro Ala Leu His Tyr Arg
145                 150                 155                 160

ttc aat gca cct att gcc cgg gat gca ttg cct ccc tac tct tgg cac   529
Phe Asn Ala Pro Ile Ala Arg Asp Ala Leu Pro Pro Tyr Ser Trp His
                165                 170                 175

tat gcc ccc tgg acc aaa tgc tca gcc cag tgt gca ggc ggc agc cag   577
Tyr Ala Pro Trp Thr Lys Cys Ser Ala Gln Cys Ala Gly Gly Ser Gln
            180                 185                 190

[illegible]   625

[illegible]   11
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   Cys Asn Thr Glu Pro Cys Pro Pro Asp Trp Val Val Gly Asn Trp Ser
   225                 230                 235                 240

   cgc tgc agc cgt agc tgt gac gct ggt gtg cgt agc cgc tca gtg gtg   769
 5 Arg Cys Ser Arg Ser Cys Asp Ala Gly Val Arg Ser Arg Ser Val Val
                   245                 250                 255

   tgc caa cgc cgg gtg tct gct gca gag gaa aaa gcc tta gac gac agt   817
   Cys Gln Arg Arg Val Ser Ala Ala Glu Glu Lys Ala Leu Asp Asp Ser
10             260                 265                 270

   gcc tgt cca cag cca cgc cca cct gtg ctg gag gcc tgc caa ggc cca   865
   Ala Cys Pro Gln Pro Arg Pro Pro Val Leu Glu Ala Cys Gln Gly Pro
          275                 280                 285
15
   atg tgc cct cct gag tgg gca acc ctg gac tgg tct gag tgt acc cca   913
   Met Cys Pro Pro Glu Trp Ala Thr Leu Asp Trp Ser Glu Cys Thr Pro
       290                 295                 300

20 agc tgt ggg cct ggt ctc cgc cac cga gtg gtc ctt tgt aag agt gca   961
   Ser Cys Gly Pro Gly Leu Arg His Arg Val Val Leu Cys Lys Ser Ala
   305                 310                 315                 320

   gat caa cga tct act ctg ccc cct ggg cac tgc ctt cct gca gcc aag  1009
25 Asp Gln Arg Ser Thr Leu Pro Pro Gly His Cys Leu Pro Ala Ala Lys
                   325                 330                 335

   cca cca tct act atg cga tgt aac ttg cgc cgc tgc cct cct gcc cgc  1057
   Pro Pro Ser Thr Met Arg Cys Asn Leu Arg Arg Cys Pro Pro Ala Arg
30             340                 345                 350

   tgg gtg acc agt gag tgg ggt gag tgt tcc aca cag tgt ggc ctc ggc  1105
   Trp Val Thr Ser Glu Trp Gly Glu Cys Ser Thr Gln Cys Gly Leu Gly
          355                 360                 365
35
   cag cag cag cgc aca gtg cgc tgc acc agc cac acc ggc cag cca tct  1153
   Gln Gln Gln Arg Thr Val Arg Cys Thr Ser His Thr Gly Gln Pro Ser
       370                 375                 380

40 cga gag tgc act gaa gcc ttg cgg cca tcc acc atg cag cag tgt gag  1201
   Arg Glu Cys Thr Glu Ala Leu Arg Pro Ser Thr Met Gln Gln Cys Glu
   385                 390                 395                 400

   gcc aag tgt gac agt gtg gtg ccg cct gga gat ggc cca gaa gaa tgc  1249
45 Ala Lys Cys Asp Ser Val Val Pro Pro Gly Asp Gly Pro Glu Glu Cys
                   405                 410                 415

   aag gat gtg aac aag gtg gct tac tgt ccc ctg gtg ctc aaa ttt cag  1297
   Lys Asp Val Asn Lys Val Ala Tyr Cys Pro Leu Val Leu Lys Phe Gln
50             420                 425                 430

   ttc tgt agc cga gcc tac ttc cgc cag atg agc tgc aaa acc tgc caa  1345
   Phe Cys Ser Arg Ala Tyr Phe Arg Gln Met Ser Cys Lys Thr Cys Gln
          435                 440                 445
55
   ggc cgc tagggtacct ggaaatcaacc tggagcacag gttgaggcag gggacatccc  1401
   Gly Arg
   450

[illegible]

tgaacagatt ttcaagtcct ctgtatattt tatcaatttg ttgggaagtg tgggaaggtg 1461
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n 1642

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<212> PRT
<213> Mus musculus ADAMTS-10

<400> 19
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Ile Cys Val Ser Gly Glu Cys Lys His Val Gly Cys Asp Arg Leu Leu
20 25 30

Gly Ser Asp Leu Arg Glu Asp Lys Cys Arg Val Cys Gly Gly Asp Gly
35 40 45

Ser Ala Cys Glu Thr Ile Glu Gly Val Phe Ser Pro Ala Leu Pro Gly
50 55 60

Thr Gly Tyr Glu Asp Val Val Trp Ile Pro Lys Gly Ser Val His Ile
65 70 75 80

Phe Ile Gln Asp Leu Asn Leu Ser Leu Ser His Leu Ala Leu Lys Gly
85 90 95

Asp Gln Glu Ser Leu Leu Leu Glu Gly Leu Pro Gly Thr Pro Gln Pro
100 105 110

Xaa Arg Leu Pro Leu Xaa Gly Thr Thr Phe His Leu Arg Gln Gly Pro
115 120 125

Asp Gln Ala Gln Ser Leu Glu Ala Leu Gly Pro Ile Asn Ala Ser Leu
130 135 140

Ile Ile Met Val Leu Ala Gln Ala Glu Leu Pro Ala Leu His Tyr Arg
145 150 155 160

Phe Asn Ala Pro Ile Ala Arg Asp Ala Leu Pro Pro Tyr Ser Trp His
165 170 175

Tyr Ala Pro Trp Thr Lys Cys Ser Ala Gln Cys Ala Gly Gly Ser Gln
180 185 190

Val Gln Val Val Glu Cys Arg Asn Gln Leu Asp Ser Ser Ala Val Ala
195 200 205

Val His Tyr Cys Ser Gly His Ser Lys Leu Pro Lys Arg Gln Arg Ala
210 215 220

Cys Asn Thr Glu Pro Cys Pro Pro Asp Trp Val Val Gly Asn Trp Ser
225 230 235 240

Arg Cys Ser Arg Ser Cys Asp Ala Gly Val Arg Ser Arg Ser Val Val
245 250 255

Val Gly Ile Ile Ala Leu Glu Asp Thr Leu Ala Gln Gln Val Pro
260 265 270

```
Ser Cys Gly Pro Gly Leu Arg His Arg Val Val Leu Cys Lys Ser Ala
305                 310                 315                 320

Asp Gln Arg Ser Thr Leu Pro Pro Gly His Cys Leu Pro Ala Ala Lys
                325                 330                 335

Pro Pro Ser Thr Met Arg Cys Asn Leu Arg Arg Cys Pro Pro Ala Arg
            340                 345                 350

Trp Val Thr Ser Glu Trp Gly Glu Cys Ser Thr Gln Cys Gly Leu Gly
        355                 360                 365

Gln Gln Gln Arg Thr Val Arg Cys Thr Ser His Thr Gly Gln Pro Ser
    370                 375                 380

Arg Glu Cys Thr Glu Ala Leu Arg Pro Ser Thr Met Gln Gln Cys Glu
385                 390                 395                 400

Ala Lys Cys Asp Ser Val Val Pro Pro Gly Asp Gly Pro Glu Glu Cys
                405                 410                 415

Lys Asp Val Asn Lys Val Ala Tyr Cys Pro Leu Val Leu Lys Phe Gln
            420                 425                 430

Phe Cys Ser Arg Ala Tyr Phe Arg Gln Met Ser Cys Lys Thr Cys Gln
        435                 440                 445

Gly Arg
    450
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<211> 1803
<212> DNA
<213> Homo sapiens ADAMTS-R1

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                                                    Met Glu
                                                     1

tgc tgc cgt cgg gca act cct ggg aca ctg ctc ctc ttc ctg gct ttc 104
Cys Cys Arg Arg Ala Thr Pro Gly Thr Leu Leu Leu Phe Leu Ala Phe
  5   10   15

ctg ctc ctg agt tcc agg acc gca cgc tcc gag gag gac cgg gac ggc 152
Leu Leu Leu Ser Ser Arg Thr Ala Arg Ser Glu Glu Asp Arg Asp Gly
 20   25   30

cta tgg gat gcc tgg ggc cca tgg agt gaa tgc tca cgc acg tgc ggg 200
Leu Trp Asp Ala Trp Gly Pro Trp Ser Glu Cys Ser Arg Thr Cys Gly
 35   40   45   50

[illegible]
[illegible]
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   cca gaa gca ggt gat ttc cga gct cag caa tgc tca gct cat aat gat   144
   Pro Glu Ala Gly Asp Phe Arg Ala Gln Gln Cys Ser Ala His Asn Asp
            85                  90                  95
5
   gtc aag cac cat ggc cag ttt tat gaa tgg ctt cct gtg tct aat gac   192
   Val Lys His His Gly Gln Phe Tyr Glu Trp Leu Pro Val Ser Asn Asp
       100                 105                 110

10 cct gac aac cca tgt tca ctc aag tgc caa gcc aaa gga aca acc ctg   240
   Pro Asp Asn Pro Cys Ser Leu Lys Cys Gln Ala Lys Gly Thr Thr Leu
   115                 120                 125                 130

   gtt gtt gaa cta gca cct aag gtc tta gat ggt acg cgt tgc tat aca   288
15 Val Val Glu Leu Ala Pro Lys Val Leu Asp Gly Thr Arg Cys Tyr Thr
                   135                 140                 145

   gaa tct ttg gat atg tgc atc agt ggt tta tgc caa att gtt ggc tgc   336
   Glu Ser Leu Asp Met Cys Ile Ser Gly Leu Cys Gln Ile Val Gly Cys
20             150                 155                 160

   gat cac cag ctg gga agc acc gtc aag gaa gat aac tgt ggg gtc tgc   384
   Asp His Gln Leu Gly Ser Thr Val Lys Glu Asp Asn Cys Gly Val Cys
           165                 170                 175
25
   aac gga gat ggg tcc acc tgc cgg ctg gtc cga ggg cag tat aaa tcc   432
   Asn Gly Asp Gly Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr Lys Ser
       180                 185                 190

30 cag ctc tcc gca acc aaa tcg gat gat act gtg gtt gca att ccc tat   480
   Gln Leu Ser Ala Thr Lys Ser Asp Asp Thr Val Val Ala Ile Pro Tyr
   195                 200                 205                 210

   gga agt aga cat att cgc ctt gtc tta aaa ggt cct gat cac tta tat   528
35 Gly Ser Arg His Ile Arg Leu Val Leu Lys Gly Pro Asp His Leu Tyr
                   215                 220                 225

   ctg gaa acc aaa acc ctc cag ggg act aaa ggt gaa aac agt ctc agc   576
   Leu Glu Thr Lys Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser Leu Ser
40             230                 235                 240

   tcc aca gga act ttc ctt gtg gac aat tct agt gtg gac ttc cag aaa   624
   Ser Thr Gly Thr Phe Leu Val Asp Asn Ser Ser Val Asp Phe Gln Lys
           245                 250                 255
45
   ttt cca gac aaa gag ata ctg aga atg gct gga ccc ttc aca gca gat   672
   Phe Pro Asp Lys Glu Ile Leu Arg Met Ala Gly Pro Leu Thr Ala Asp
       260                 265                 270

50 ttc att gtc aag att cgt aac tcg ggt tcc gct gac agt acc aca gtc cag   720
   Phe Ile Val Lys Ile Arg Asn Ser Gly Ser Ala Asp Ser Thr Val Gln
   275                 280                 285                 290

   ttc atc ttc tat caa ccc atc atc cac cga tgg agg gag acg gat ttc   768
55 Phe Ile Phe Tyr Gln Pro Ile Ile His Arg Trp Arg Glu Thr Asp Phe
                   295                 300                 305

   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...   816

   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...   864

   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...   912

   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...   960

   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...  1008
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```
   His Tyr Tyr Pro Glu Asn Ile Lys Pro Lys Pro Lys Leu Gln Glu Cys
       340                 345                 350

   aac ttg gat cct tgt cca gcc agt gac gga tac aag cag atc atg cct   1150
 5 Asn Leu Asp Pro Cys Pro Ala Ser Asp Gly Tyr Lys Gln Ile Met Pro
   355                 360                 365                 370

   tat gac ctc tac cat ccc ctt cct cgg tgg gag gcc acc cca tgg acc   1200
   Tyr Asp Leu Tyr His Pro Leu Pro Arg Trp Glu Ala Thr Pro Trp Thr
10                 375                 380                 385

   gcg tgc tcc tcc tcg tgt ggg ggg ggc atc cag agc cgg gca gtt tcc   1250
   Ala Cys Ser Ser Ser Cys Gly Gly Gly Ile Gln Ser Arg Ala Val Ser
               390                 395                 400
15
   tgt gtg gag gag gac atc cag ggg cat gtc act tca gtg gaa gag tgg   1300
   Cys Val Glu Glu Asp Ile Gln Gly His Val Thr Ser Val Glu Glu Trp
           405                 410                 415

20 aaa tgc atg tac acc cct aag atg ccc atc gcg cag ccc tgc aac att   1350
   Lys Cys Met Tyr Thr Pro Lys Met Pro Ile Ala Gln Pro Cys Asn Ile
       420                 425                 430

   ttt gac tgc cct aaa tgg ctg gca cag gag tgg tct ccg tgc aca gtg   1400
25 Phe Asp Cys Pro Lys Trp Leu Ala Gln Glu Trp Ser Pro Cys Thr Val
   435                 440                 445                 450

   acg tgt ggc cag ggc ctc aga tac cgt gtg gtc ctc tgc atc gac cat   1450
   Thr Cys Gly Gln Gly Leu Arg Tyr Arg Val Val Leu Cys Ile Asp His
30                 455                 460                 465

   cga gga atg cac aca gga ggc tgt agc cca aaa aca aag ccc cac ata   1500
   Arg Gly Met His Thr Gly Gly Cys Ser Pro Lys Thr Lys Pro His Ile
               470                 475                 480
35
   aaa gag gaa tgc atc gta ccc act ccc tgc tat aaa ccc aaa gag aaa   1550
   Lys Glu Glu Cys Ile Val Pro Thr Pro Cys Tyr Lys Pro Lys Glu Lys
           485                 490                 495

40 ctt cca gtc gag gcc aag ttg cca tgg ttc aaa caa gct caa gag cta   1600
   Leu Pro Val Glu Ala Lys Leu Pro Trp Phe Lys Gln Ala Gln Glu Leu
       500                 505                 510

   gaa gaa gga gct gct gtg tca gag gag ccc tcg taa gtt gta           1650
45 Glu Glu Gly Ala Ala Val Ser Glu Glu Pro Ser     Val Val
   515                 520                 525

   aaaggaaaga ctgtttctat tttgaaactt ttgttttaag aaaagtagtg ttcaatggtt 1710

91 gtagttttca tgggttatga actaagtgta atattttaat taaagttttt ggggattaaa 1770

   atttaaagatt gatttagtttc aaaaaaaaaa aaaaaaaaga tgcggccgc           1823

95 <210> 21
   <211> 525
   <212> PRT
   <213> Homo sapiens IFNWTS-B1

Arg Asp Leu Trp Arg Val Trp Gly Leu Ile Pro Leu Tyr Arg
          35                  40                  45
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Cys Gly Gly Gly Ala Ala Asn Ser Leu Arg Arg Cys Leu Ser Ser Lys
        50                  55                  60
Ser Cys Glu Gly Arg Asn Ile Arg Tyr Arg Thr Cys Ser Asn Val Asp
 65                  70                  75                  80
Cys Pro Pro Glu Ala Gly Asp Phe Arg Ala Gln Gln Cys Ser Ala His
                85                  90                  95
Asn Asp Val Lys His His Gly Gln Phe Tyr Glu Trp Leu Pro Val Ser
            100                 105                 110
Asn Asp Pro Asp Asn Pro Cys Ser Leu Lys Cys Gln Ala Lys Gly Thr
        115                 120                 125
Thr Leu Val Val Glu Leu Ala Pro Lys Val Leu Asp Gly Thr Arg Cys
    130                 135                 140
Tyr Thr Glu Ser Leu Asp Met Cys Ile Ser Gly Leu Cys Gln Ile Val
145                 150                 155                 160
Gly Cys Asp His Gln Leu Gly Ser Thr Val Lys Glu Asp Asn Cys Gly
                165                 170                 175
Val Cys Asn Gly Asp Gly Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr
            180                 185                 190
Lys Ser Gln Leu Ser Ala Thr Lys Ser Asp Asp Thr Val Val Ala Ile
        195                 200                 205
Pro Tyr Gly Ser Arg His Ile Arg Leu Val Leu Lys Gly Pro Asp His
    210                 215                 220
Leu Tyr Leu Glu Thr Lys Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser
225                 230                 235                 240
Leu Ser Ser Thr Gly Thr Phe Leu Val Asp Asn Ser Ser Val Asp Phe
                245                 250                 255
Gln Lys Phe Pro Asp Lys Glu Ile Leu Arg Met Ala Gly Pro Leu Thr
            260                 265                 270
Ala Asp Phe Ile Val Lys Ile Arg Asn Ser Gly Ser Ala Asp Ser Thr
        275                 280                 285
Val Gln Phe Ile Phe Tyr Gln Pro Ile Ile His Arg Trp Arg Glu Thr
    290                 295                 300
Asp Phe Phe Pro Cys Ser Ala Thr Cys Gly Gly Gly Tyr Gln Leu Thr
305                 310                 315                 320
Ser Ala Glu Cys Tyr Asp Leu Arg Ser Asn Arg Val Val Ala Asp Gln
                325                 330                 335
Tyr Cys His Tyr Tyr Pro Glu Asn Ile Lys Pro Lys Pro Lys Leu Gln
            340                 345                 350
Glu Cys Asn Leu Asp Pro Cys Pro Ala Ser Asp Gly Tyr Lys Gln Ile
        355                 360                 365
Met Pro Tyr Asp Leu Tyr His Pro Leu Pro Arg Trp Glu Ala Thr Pro
    370                 375                 380
Trp Thr Ala Cys Ser Ser Ser Cys Gly Gly Gly Ile Gln Ser Arg Ala
385                 390                 395                 400
Val Ser Cys Val Glu Glu Asp Ile Gln Gly His Val Thr Ser Val Glu
                405                 410                 415
Glu Trp Lys Cys Met Tyr Thr Pro Lys Met Pro Ile Ala Gln Pro Cys
            420                 425                 430
Asn Ile Phe Asp Cys Pro Lys Trp Leu Ala Gln Glu Trp Ser Pro Cys
        435                 440                 445
Thr Val Thr Cys Gly Gln Gly Leu Arg Tyr Arg Val Val Leu Cys Ile
    450                 455                 460
Asp His Arg Gly Met His Thr Gly Gly Cys Ser Pro Lys Thr Lys Pro
465                 470                 475                 480
His Ile Lys Glu Glu Cys Ile Val Pro Thr Pro Cys Tyr Lys Pro Lys
                485                 490                 495
Glu Lys Leu Pro Val Glu Ala Lys Leu Pro Trp Phe Lys Gln Ala Gln
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(2) INFORMATION FOR SEQ ID NO:
    (i) SEQUENCE CHARACTERISTICS:
    (ii) MOLECULE TYPE:
    (iii) HYPOTHETICAL:
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<213> Homo sapiens ADAMTS-5

<400> 22

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Gly His Leu Leu Gly Leu Ser His Asp Asp Ser Lys Phe Cys Glu Glu
 1               5                  10                  15

Thr Phe Gly Ser Thr Glu Asp Lys Arg Leu Met Ser Ser Ile Leu Thr
            20                  25                  30

Ser Ile Asp Ala Ser Lys Pro Trp Ser Lys Cys Thr Ser Ala Thr Ile
        35                  40                  45

Thr Glu Phe Leu Asp Asp Gly His Gly Asn Cys Leu Leu Asp Leu Pro
    50                  55                  60

Arg Lys Gln Ile Leu Gly Pro Glu Glu Leu Pro Gly Gln Thr Tyr Asp
65                  70                  75                  80

Ala Thr Gln Gln Cys Asn Leu Thr Phe Gly Pro Asp Tyr Ser Val Cys
                85                  90                  95

Pro Gly Xaa Asp Val Cys Ala Arg Leu Trp Cys Ala Val Val Arg Gln
            100                 105                 110

Gly Gln Met Val Cys Leu Thr Lys Lys Leu Pro Ala Val Glu Gly Thr
        115                 120                 125

Pro Cys Gly Lys Gly Arg Ile Cys Leu Gln Gly Lys Cys Val Asp Lys
    130                 135                 140

Thr Lys Lys Lys Tyr Tyr Ser Thr Ser Ser His Gly Asn Trp Gly Ser
145                 150                 155                 160

Trp Gly Ser Trp Gly Gln Cys Ser Arg Ser Cys Gly Gly Gly Val Gln
                165                 170                 175

Phe Ala Tyr Arg His Cys Asn Asn Pro Ala Pro Arg Asn Asn Gly Arg
            180                 185                 190

Tyr Cys Thr Gly Lys Arg Ala Ile Tyr His Ser Cys Ser Leu Met Pro
        195                 200                 205

Cys Pro Pro Asn Gly Lys Ser Phe Arg His Glu Gln Cys Glu Ala Lys
    210                 215                 220

Asn Gly Tyr Gln Ser Asp Ala Lys Gly Val Lys Thr Phe Val Glu Trp
225                 230                 235                 240

Val Pro Lys Tyr Ala Gly Val Leu Pro Ala Asp Val Cys Lys Leu Thr
                245                 250                 255

Cys Arg Ala Lys Gly Thr Gly Tyr Tyr Val Val Phe Ser Pro Lys Val
            260                 265                 270

Thr Asp Gly Thr Gln Cys Arg Pro Tyr Ser Asn Ser Val Cys Val Arg
        275                 280                 285
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Val Arg Ile Pro Glu Gly Ala Thr His Ile Lys Val Arg Gln Phe Lys
340 345 350

Ala Lys Asp Gln Thr Arg Phe Thr Ala Tyr Leu Ala Leu Lys Lys Lys
355 360 365

Asn Gly Glu Tyr Leu Ile Asn Gly Lys Tyr Met Ile Ser Thr Ser Glu
370 375 380

Thr Ile Ile Asp Ile Asn Gly Thr Val Met Asn Tyr Ser Gly Trp Ser
385 390 395 400

His Arg Asp Asp Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys Glu
405 410 415

Ile Leu Ile Val Gln Ile Leu Ala Thr Asp Pro Thr Lys Pro Leu Asp
420 425 430

Val Arg Tyr Ser Phe Phe Val Pro Lys Lys Ser Thr Pro Lys Val Asn
435 440 445

Ser Val Thr Ser His Gly Ser Asn Lys Val Gly Ser His Thr Ser Gln
450 455 460

Pro Gln Trp Val Thr Gly Pro Trp Leu Ala Cys Ser Arg Thr Cys Asp
465 470 475 480

Thr Gly Trp His Thr Arg Thr Val Gln Cys Gln Asp Gly Asn Arg Lys
485 490 495

Leu Ala Lys Gly Cys Pro Leu Ser Gln Arg Pro Ser Ala Phe Lys Gln
500 505 510

Cys Leu Leu Lys Lys Cys
515

<210> 23
<211> 3409
<212> DNA
<213> Homo sapiens ADAMTS-10

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<221> CDS
<222> (25)..(3240)

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Met Ser Ser Cys Ser Val Trp Arg Ala
1 5

atg aga tcg cct tcc tca ccc gcg tgg acc aca acg ggg cac tgc tgg 99
Met Arg Ser Pro Ser Pro Pro Ala Trp Thr Thr Thr Gly His Cys Trp
10 15 20 25

cct tct cgc cac ctc ctc cct gga gca gcg ccg tgg cac ggg ggc cac 147
Pro Ser Arg His Leu Leu Pro Gly Ala Ala Pro Arg His Gly Gly His
30 35 40

Leu Leu Arg Leu Thr Ala Ser Tyr Arg Thr Ala Asn Arg Arg Val
45 50

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   gtg gag tac tgg aca cgg gag ggc ctg gcc tgg cag agg gcg gcc cgg   291
   Val Glu Tyr Trp Thr Arg Glu Gly Leu Ala Trp Gln Arg Ala Ala Arg
        75                  80                  85
5
   ccc cac tgc ctc tac gct ggt cac ctg cag ggc cag gcc agc agc tcc   339
   Pro His Cys Leu Tyr Ala Gly His Leu Gln Gly Gln Ala Ser Ser Ser
    90                  95                 100                 105

10 cat gtg gcc atc agc acc tgt gga ggc ctg cac ggc ctg atc gtg gca   387
   His Val Ala Ile Ser Thr Cys Gly Gly Leu His Gly Leu Ile Val Ala
                   110                 115                 120

   gac gag gaa gag tac ctg att gag ccc ctg cac ggt ggg ccc aag ggt   435
15 Asp Glu Glu Glu Tyr Leu Ile Glu Pro Leu His Gly Gly Pro Lys Gly
               125                 130                 135

   tct cgg agc ccg gag gaa agt gga cca cat gtg gtg tac aag cgt tcc   483
   Ser Arg Ser Pro Glu Glu Ser Gly Pro His Val Val Tyr Lys Arg Ser
20         140                 145                 150

   tct ctg cgt cac ccc cac ctg gac aca gcc tgt gga gtg aga gat gag   531
   Ser Leu Arg His Pro His Leu Asp Thr Ala Cys Gly Val Arg Asp Glu
       155                 160                 165
25
   aaa ccg tgg aaa ggg cgg cca tgg tgg ctg cgg acc ttg aag cca ccg   579
   Lys Pro Trp Lys Gly Arg Pro Trp Trp Leu Arg Thr Leu Lys Pro Pro
   170                 175                 180                 185

30 cct gcc aga ccc ctg ggg aat gaa aca gag cgt ggt cag cca ggc ctg   627
   Pro Ala Arg Pro Leu Gly Asn Glu Thr Glu Arg Gly Gln Pro Gly Leu
                   190                 195                 200

   aag cga tcg gtc agc cga gag cgc tac gtg gag acc ctg gtg gtg gct   675
35 Lys Arg Ser Val Ser Arg Glu Arg Tyr Val Glu Thr Leu Val Val Ala
               205                 210                 215

   gac aag atg atg gtg gcc tat cac ggg cgc cgg gat gtg gag cag tat   723
   Asp Lys Met Met Val Ala Tyr His Gly Arg Arg Asp Val Glu Gln Tyr
40         220                 225                 230

   gtc ctg gcc atc atg aac att gtt gcc aaa ctt ttc cag gac tcg agt   771
   Val Leu Ala Ile Met Asn Ile Val Ala Lys Leu Phe Gln Asp Ser Ser
       235                 240                 245
45
   ctg gga agc acc gtt aac atc ctc gta act cgc ctt atc ctg ctt acg   819
   Leu Gly Ser Thr Val Asn Ile Leu Val Thr Arg Leu Ile Leu Leu Thr
   250                 255                 260                 265

50 gag gac cag ccg acg ctg gag atc acg cac cat gcg ggg aag tcc ttg   867
   Glu Asp Gln Pro Thr Leu Glu Ile Thr His His Ala Gly Lys Ser Leu
                   270                 275                 280

   gac agc ttc tgt aag tgg cag aaa tcc atc gtg aac cac agc ggc cat   915
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 5  Ala Ala Ser Met Arg Thr Leu Ala Ala Thr Ser Val His His Cys His
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    Glu Ile Gly His Thr Phe Gly Met Asn His Asp Gly Val Gly Asn Ser
10              365                 370                 375

    tgt ggg gcc cgt ggt cag gac cca gcc aag ctc atg gct gcc cac att   1203
    Cys Gly Ala Arg Gly Gln Asp Pro Ala Lys Leu Met Ala Ala His Ile
            380                 385                 390
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    acc atg aag acc aac cca ttc gtg tgg tca tcc tgc aac cgt gac tac   1251
    Thr Met Lys Thr Asn Pro Phe Val Trp Ser Ser Cys Asn Arg Asp Tyr
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20  atc acc agc ttt cta gac tcg ggc ctg ggg ctc tgc ctg aac aac cgg   1299
    Ile Thr Ser Phe Leu Asp Ser Gly Leu Gly Leu Cys Leu Asn Asn Arg
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    ccc ccc aga cag gac ttt gtg tac ccg aca gtg gca ccg ggc caa gcc   1347
25  Pro Pro Arg Gln Asp Phe Val Tyr Pro Thr Val Ala Pro Gly Gln Ala
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    Tyr Asp Ala Asp Glu Gln Cys Arg Phe Gln His Gly Val Lys Ser Arg
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    cag tgt aaa tac ggg gag gtc tgc agc gag ctg tgg tgt ctg agc aag   1443
    Gln Cys Lys Tyr Gly Glu Val Cys Ser Glu Leu Trp Cys Leu Ser Lys
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    agc aac cgg tgc atc acc aac agc atc ccg gcc gcc gag ggc acg ctg   1491
    Ser Asn Arg Cys Ile Thr Asn Ser Ile Pro Ala Ala Glu Gly Thr Leu
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40  tgc cag acg cac acc atc gac aag ggg tgg tgc tac aaa cgg gtc tgt   1539
    Cys Gln Thr His Thr Ile Asp Lys Gly Trp Cys Tyr Lys Arg Val Cys
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    gtc ccc ttt ggg tcg cgc cca gag ggt gtg gac gga gcc tgg ggg ccg   1587
45  Val Pro Phe Gly Ser Arg Pro Glu Gly Val Asp Gly Ala Trp Gly Pro
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    Trp Thr Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly Gly Val Ser
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    tct tct agt cgt cac tgc gac agc ccc agg cca acc atc ggg ggc aag   1683
    Ser Ser Ser Arg His Cys Asp Ser Pro Arg Pro Thr Ile Gly Gly Lys
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    aac ttc tac acg gag agg gcg gca gcc gtg gtg gac ggg aca ccc tgc   1923
    Asn Phe Tyr Thr Glu Arg Ala Ala Ala Val Val Asp Gly Thr Pro Cys
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10  cgt cca gac acg gtg gac att tgc gtc agt ggc gaa tgc aag cac gtg   1971
    Arg Pro Asp Thr Val Asp Ile Cys Val Ser Gly Glu Cys Lys His Val
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    ggc tgc gac cga gtc ctg ggc tcc gac ctg cgg gag gac aag tgc cga   2019
15  Gly Cys Asp Arg Val Leu Gly Ser Asp Leu Arg Glu Asp Lys Cys Arg
    650                 655                 660                 665

    gtg tgt ggc ggt gac ggc agt gcc tgc gag acc atc gag ggc gtc ttc   2067
    Val Cys Gly Gly Asp Gly Ser Ala Cys Glu Thr Ile Glu Gly Val Phe
20                  670                 675                 680

    agc cca gcc tca cct ggg gcc ggg tac gag gat gtc gtc tgg att ccc   2115
    Ser Pro Ala Ser Pro Gly Ala Gly Tyr Glu Asp Val Val Trp Ile Pro
                685                 690                 695
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    aaa ggc tcc gtc cac atc ttc atc cag gat ctg aac ctc tct ctc agt   2163
    Lys Gly Ser Val His Ile Phe Ile Gln Asp Leu Asn Leu Ser Leu Ser
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    His Leu Ala Leu Lys Gly Asp Gln Glu Ser Leu Leu Leu Glu Gly Leu
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    cct ggg acc ccc cag ccc cac cgt ctg cct cta gct ggg acc acc ttt   2259
35  Pro Gly Thr Pro Gln Pro His Arg Leu Pro Leu Ala Gly Thr Thr Phe
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    caa ctg cga cag ggg cca gac cag gtc cag agc ctc gaa gcc ctg gga   2307
    Gln Leu Arg Gln Gly Pro Asp Gln Val Gln Ser Leu Glu Ala Leu Gly
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    ccg att aat gca tct ctc atc gtc atg gtg ctg gcc cgg acc gag ctg   2355
    Pro Ile Asn Ala Ser Leu Ile Val Met Val Leu Ala Arg Thr Glu Leu
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    cct gcc ctc cgc tac cgc ttc aat gcc ccc atc gcc cgt gac tcg ctg   2403
    Pro Ala Leu Arg Tyr Arg Phe Asn Ala Pro Ile Ala Arg Asp Ser Leu
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50  ccc ccc tac tcc tgg cac tat gcg ccc tgg acc aag tgc tcg gcc cag   2451
    Pro Pro Tyr Ser Trp His Tyr Ala Pro Trp Thr Lys Cys Ser Ala Gln
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    tgt gca ggc ggt agc cag gtg cag gcg gtg gag tgc cgc aac cag ctg   2499
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 5 Arg Ser Arg Ser Val Val Cys Gln Arg Arg Val Ser Ala Ala Glu Glu
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   aag gcg ctg gac gac agc gca tgc ccg cag ccg cgc cca cct gta ctg   2739
   Lys Ala Leu Asp Asp Ser Ala Cys Pro Gln Pro Arg Pro Pro Val Leu
10 890                 895                 900                 905

   gag gcc tgc cac ggc ccc act tgc cct ccg gag tgg gcg gcc ctc gac   2787
   Glu Ala Cys His Gly Pro Thr Cys Pro Pro Glu Trp Ala Ala Leu Asp
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   tgg tct gag tgc acc ccc agc tgc ggg ccg ggc ctc cgc cac cgc gtg   2835
   Trp Ser Glu Cys Thr Pro Ser Cys Gly Pro Gly Leu Arg His Arg Val
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20 gtc ctt tgc aag agc gca gac cac cgc gcc acg ctg ccc ccg gcg cac   2883
   Val Leu Cys Lys Ser Ala Asp His Arg Ala Thr Leu Pro Pro Ala His
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   tgc tca ccc gcc gcc aag cca ccg gct acc atg cgc tgc aac ttg cgc   2931
25 Cys Ser Pro Ala Ala Lys Pro Pro Ala Thr Met Arg Cys Asn Leu Arg
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   cgc tgc ccc ccg gcc cgc tgg gtg gct ggc gag tgg ggt gag tgc tct   2979
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   gca cag tgc ggc gtc ggg cag cgg cag cgc tcg gtg cgc tgc acc agc   3027
   Ala Gln Cys Gly Val Gly Gln Arg Gln Arg Ser Val Arg Cys Thr Ser
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   cac acg ggc cag gcg tcg cac gag tgc acg gag gcc ctg cgg ccg ccc   3075
   His Thr Gly Gln Ala Ser His Glu Cys Thr Glu Ala Leu Arg Pro Pro
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40 acc acg cag cag tgt gag gcc aag tgc gac agc cca acc ccc ggg gac   3123
   Thr Thr Gln Gln Cys Glu Ala Lys Cys Asp Ser Pro Thr Pro Gly Asp
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45 Gly Pro Glu Glu Cys Lys Asp Val Asn Lys Val Ala Tyr Cys Pro Leu
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Gly Ala Ala Pro Arg His Gly Gly His Ser Arg Val Pro Pro Leu Leu
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Gln Ser Gly Leu Ala Ser Thr His Phe Leu Leu Asn Leu Thr Arg Ser
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Ser Arg Leu Leu Ala Gly Arg Val Ser Val Glu Tyr Trp Thr Arg Glu
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Gly Leu Ala Trp Gln Arg Ala Ala Arg Pro His Cys Leu Tyr Ala Gly
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His Leu Gln Gly Gln Ala Ser Ser Ser His Val Ala Ile Ser Thr Cys
            100                 105                 110

Gly Gly Leu His Gly Leu Ile Val Ala Asp Glu Glu Glu Tyr Leu Ile
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Glu Pro Leu His Gly Gly Pro Lys Gly Ser Arg Ser Pro Glu Glu Ser
    130                 135                 140

Gly Pro His Val Val Tyr Lys Arg Ser Ser Leu Arg His Pro His Leu
145                 150                 155                 160

Asp Thr Ala Cys Gly Val Arg Asp Glu Lys Pro Trp Lys Gly Arg Pro
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Trp Trp Leu Arg Thr Leu Lys Pro Pro Pro Ala Arg Pro Leu Gly Asn
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Glu Thr Glu Arg Gly Gln Pro Gly Leu Lys Arg Ser Val Ser Arg Glu
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Arg Tyr Val Glu Thr Leu Val Val Ala Asp Lys Met Met Val Ala Tyr
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His Gly Arg Arg Asp Val Glu Gln Tyr Val Leu Ala Ile Met Asn Ile
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Val Ala Lys Leu Phe Gln Asp Ser Ser Leu Gly Ser Thr Val Asn Ile
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Leu Val Thr Arg Leu Ile Leu Leu Thr Glu Asp Gln Pro Thr Leu Glu
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Ile Thr His His Ala Gly Lys Ser Leu Asp Ser Phe Cys Lys Trp Gln
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Lys Ser Ile Val Asn His Ser Gly His Gly Asn Ala Ile Pro Glu Asn
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Ala Glu Cys Val Ser Ala Arg Glu Ala Ala Ala Ser Met Asp Thr Leu
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Met Asn His Asp Gly Val Gly Asn Ser Cys Gly Ala Arg Gly Gln Asp
370 375 380

Pro Ala Lys Leu Met Ala Ala His Ile Thr Met Lys Thr Asn Pro Phe
385 390 395 400

Val Trp Ser Ser Cys Asn Arg Asp Tyr Ile Thr Ser Phe Leu Asp Ser
405 410 415

Gly Leu Gly Leu Cys Leu Asn Asn Arg Pro Pro Arg Gln Asp Phe Val
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Tyr Pro Thr Val Ala Pro Gly Gln Ala Tyr Asp Ala Asp Glu Gln Cys
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Arg Phe Gln His Gly Val Lys Ser Arg Gln Cys Lys Tyr Gly Glu Val
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Cys Ser Glu Leu Trp Cys Leu Ser Lys Ser Asn Arg Cys Ile Thr Asn
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Lys Gly Trp Cys Tyr Lys Arg Val Cys Val Pro Phe Gly Ser Arg Pro
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Glu Gly Val Asp Gly Ala Trp Gly Pro Trp Thr Pro Trp Gly Asp Cys
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Ser Pro Arg Pro Thr Ile Gly Gly Lys Tyr Cys Leu Gly Glu Arg Arg
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Phe Arg Glu Val Gln Cys Ser Glu Phe Asp Ser Ile Pro Phe Arg Gly
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Lys Phe Tyr Lys Trp Lys Thr Tyr Arg Gly Gly Gly Val Lys Ala Cys
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Ser Leu Thr Ser Leu Ala Glu Gly Phe Asn Phe Tyr Thr Glu Arg Ala
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Ala Ala Val Val Asp Gly Thr Pro Cys Arg Pro Asp Thr Val Asp Ile
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Cys Val Ser Gly Glu Cys Lys His Val Gly Cys Asp Arg Val Leu Gly

Gly Tyr Glu Asp Val Val Trp Ile Pro Lys Gly Ser Val His Ile Trp

690 695 700

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Arg Leu Pro Leu Ala Gly Thr Thr Phe Gln Leu Arg Gln Gly Pro Asp
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Val Met Val Leu Ala Arg Thr Glu Leu Pro Ala Leu Arg Tyr Arg Phe
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Ala Pro Trp Thr Lys Cys Ser Ala Gln Cys Ala Gly Gly Ser Gln Val
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Gln Ala Val Glu Cys Arg Asn Gln Leu Asp Ser Ser Ala Val Ala Pro
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His Tyr Cys Ser Ala His Ser Lys Leu Pro Lys Arg Gln Arg Ala Cys
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Cys Pro Gln Pro Arg Pro Pro Val Leu Glu Ala Cys His Gly Pro Thr
900 905 910

Cys Pro Pro Glu Trp Ala Ala Leu Asp Trp Ser Glu Cys Thr Pro Ser
915 920 925

Cys Gly Pro Gly Leu Arg His Arg Val Val Leu Cys Lys Ser Ala Asp
930 935 940

His Arg Ala Thr Leu Pro Pro Ala His Cys Ser Pro Ala Ala Lys Pro
945 950 955 960

Pro Ala Thr Met Arg Cys Asn Leu Arg Arg Cys Pro Pro Ala Arg Trp
965 970 975

Val Ala Gly Glu Trp Gly Glu Cys Ser Ala Gln Cys Gly Val Gly Gln
980 985 990

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995 1000 1005

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   gac gcc gcg gcg gcc gtg cgc aag gac agg ctg cac ccg agg caa gtg   149
   Asp Ala Ala Ala Ala Val Arg Lys Asp Arg Leu His Pro Arg Gln Val
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30 aaa tta tta gag acc ctg agc gaa tac gaa atc gtg tct ccc atc cga   197
   Lys Leu Leu Glu Thr Leu Ser Glu Tyr Glu Ile Val Ser Pro Ile Arg
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35 Val Asn Ala Leu Gly Glu Pro Phe Pro Thr Asn Val His Phe Lys Arg
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   acg cga cgg agc att aac tct gcc act gac ccc tgg cct gcc ttc gcc   293
   Thr Arg Arg Ser Ile Asn Ser Ala Thr Asp Pro Trp Pro Ala Phe Ala
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   tcc tcc tct tcc tcc tct acc tcc ccc cag gcg cat tac cgc ctc tct   341
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   gcc ttc ggc cag cag ttt cta ttt aat ctc acc gcc aat gct gga ttt   389
   Ala Phe Gly Gln Gln Phe Leu Phe Asn Leu Thr Ala Asn Ala Gly Phe
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50 atc gct cca ctg ttc act gtc acg ctc ctc ggg acg ccc agg gtg aat   437
   Ile Ala Pro Leu Phe Thr Val Thr Leu Leu Gly Thr Pro Gly Val Asn
   120                 125                 130                 135

   cag acc aag ttt tat tcc gaa gag gaa gcg gaa ctc aag cac tgt ttc   485
55 Gln Thr Lys Phe Tyr Ser Glu Glu Glu Ala Glu Leu Lys His Cys Phe
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Gln Asn Lys Pro His Ile Ile Tyr Arg Arg Ser Ala Pro Gln Arg Glu
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Pro Ser Thr Gly Arg His Ala Cys Asp Thr Ser Glu His Lys Asn Arg
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His Ser Lys Asp Lys Lys Lys Thr Arg Ala Arg Lys Trp Gly Glu Arg
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   gga aag ttg tac aac ccc gat gta cgc tat tct ttc aat att cca att   2645
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                  860                 865                 870

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   Glu Asp Lys Pro Gln Gln Phe Tyr Trp Asn Ser His Gly Pro Trp Gln
                  875                 880                 885

   gca tgc agt aaa ccc tgc caa ggg gaa cgg aaa cga aaa ctt gtt tgc   2741
45 Ala Cys Ser Lys Pro Cys Gln Gly Glu Arg Lys Arg Lys Leu Val Cys
         890                 895                 900

   act agg gaa tct gat cag ctt act gtt tct gat caa aga tgc gat cgg   2789
   Thr Arg Glu Ser Asp Gln Leu Thr Val Ser Asp Gln Arg Cys Asp Arg
50     905                 910                 915

   ctg ccc cag cct gga cac att act gaa ccc tgt ggt aca ggc tgt gac   2837
   Leu Pro Gln Pro Gly His Ile Thr Glu Pro Cys Gly Thr Gly Cys Asp
   920                 925                 930                 935
55
   gtg agg tgg cat gtt gcc agc agg agt gaa tgt agt gcc cag tgt ggc   2885
   Leu Arg Trp His Val Ala Ser Arg Ser Glu Cys Ser Ala Gln Cys Gly
                  940                 945                 950

   [illegible]   2933
   [illegible]
                  955                 960                 965
```

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   aaa cca agc aac cgt gaa aaa tgc tca ggg gaa tgt aac acg ggt ggc   3029
   Lys Pro Ser Asn Arg Glu Lys Cys Ser Gly Glu Cys Asn Thr Gly Gly
       985                 990                 995
5
   tgg cgc tat tct gcc tgg act gaa tgt tca aaa agc tgt gac ggt ggg   3077
   Trp Arg Tyr Ser Ala Trp Thr Glu Cys Ser Lys Ser Cys Asp Gly Gly
  1000                1005                1010                1015

10 acc cag agg aga agg gct att tgt gtc aat acc cga aat gat gta ctg   3125
   Thr Gln Arg Arg Arg Ala Ile Cys Val Asn Thr Arg Asn Asp Val Leu
                   1020                1025                1030

   gat gac agc aaa tgc aca cat caa gag aaa gtt acc att cag agg tgc   3173
15 Asp Asp Ser Lys Cys Thr His Gln Glu Lys Val Thr Ile Gln Arg Cys
               1035                1040                1045

   agt gag ttc cct tgt cca cag tgg aaa tct gga gac tgg tca gag tgc   3221
   Ser Glu Phe Pro Cys Pro Gln Trp Lys Ser Gly Asp Trp Ser Glu Cys
20        1050                1055                1060

   ttg gtc acc tgt gga aaa ggg cat aag cac cgc cag gtc tgg tgt cag   3269
   Leu Val Thr Cys Gly Lys Gly His Lys His Arg Gln Val Trp Cys Gln
      1065                1070                1075
25
   ttt ggt gaa gat cga tta aat gat aga atg tgt gac cct gag acc aag   3317
   Phe Gly Glu Asp Arg Leu Asn Asp Arg Met Cys Asp Pro Glu Thr Lys
   1080                1085                1090                1095

30 cca aca tct atg cag act tgt cag cag ccg gaa atg gca tcc tgg cag   3365
   Pro Thr Ser Met Gln Thr Cys Gln Gln Pro Glu Met Ala Ser Trp Gln
                   1100                1105                1110

   gcg ggt ccc tgg gta cag tgc agt gtc act tgt gga cag gga tac cag   3413
35 Ala Gly Pro Trp Val Gln Cys Ser Val Thr Cys Gly Gln Gly Tyr Gln
               1115                1120                1125

   cta aga gca gtg aaa tgc atc att ggg act tat atg tca gtg gta gat   3461
   Leu Arg Ala Val Lys Cys Ile Ile Gly Thr Tyr Met Ser Val Val Asp
40        1130                1135                1140

   gac aat gac tgt aat gca gca act aga cca act gat acc cag gac tgt   3509
   Asp Asn Asp Cys Asn Ala Ala Thr Arg Pro Thr Asp Thr Gln Asp Cys
      1145                1150                1155
45
   gaa tta cca tca tgt cat cct ccc cca gct gcg ccg gaa acg agg aga   3557
   Glu Leu Pro Ser Cys His Pro Pro Pro Ala Ala Pro Glu Thr Arg Arg
   1160                1165                1170                1175

50 agc aca tac agt gca gca aga ccc agg tgg cga ttt ggg tct tgg acc   3605
   Ser Thr Tyr Ser Ala Pro Arg Thr Gln Trp Arg Phe Gly Ser Trp Thr
                   1180                1185                1190

   cca tgc tca gcc act tgt ggg aaa ggt acc cgg atg aga tac gtc agc   3653
55 Pro Cys Ser Ala Thr Cys Gly Lys Gly Thr Arg Met Arg Tyr Val Ser
               1195                1200                1205

   tgc cga aat gag aat ggt tgt gtg gct gac gat agt gcc tgt gct aac   3701

   ...                 ..                  ..
60
   cag tgg aag gca ttg gat tgg ggg ttt tgt tct gtg act tgt ggg ttg
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   Gln Trp Lys Ala Leu Asp Trp Ser Ser Cys Ser Val Thr Cys Gly Gln
   1240               1245                1250                1255

   ggt agg gca acc cgg caa gtg atg tgt gtc aac tac agt gac cac gtg   3845
 5 Gly Arg Ala Thr Arg Gln Val Met Cys Val Asn Tyr Ser Asp His Val
                  1260                1265                1270

   atc gat cgg agt gag tgt gac cag gat tat atc cca gaa act gac cag   3893
   Ile Asp Arg Ser Glu Cys Asp Gln Asp Tyr Ile Pro Glu Thr Asp Gln
10            1275                1280                1285

   gac tgt tcc atg tca cca tgc cct caa agg acc cca gac agt ggc tta   3941
   Asp Cys Ser Met Ser Pro Cys Pro Gln Arg Thr Pro Asp Ser Gly Leu
         1290                1295                1300
15
   gct cag cac ccc ttc caa aat gag gac tat cgt ccc cgg agc gcc agc   3989
   Ala Gln His Pro Phe Gln Asn Glu Asp Tyr Arg Pro Arg Ser Ala Ser
      1305                1310                1315

20 ccc agc cgc acc cat gtg ctc ggt gga aac cag tgg aga act ggc ccc   4037
   Pro Ser Arg Thr His Val Leu Gly Gly Asn Gln Trp Arg Thr Gly Pro
   1320               1325                1330                1335

   tgg gga gca tgt tcc agt acc tgt ggt ggc gga tcc cag cgg cgt gtt   4085
25 Trp Gly Ala Cys Ser Ser Thr Cys Ala Gly Gly Ser Gln Arg Arg Val
                  1340                1345                1350

   gtt gta tgt cag gat gaa aat gga tac acc gca aac gac tgt gtg gag   4133
   Val Val Cys Gln Asp Glu Asn Gly Tyr Thr Ala Asn Asp Cys Val Glu
30            1355                1360                1365

   aga ata aaa cct gat gag caa aga gcc tgt gaa tcc ggc cct tgt cct   4181
   Arg Ile Lys Pro Asp Glu Gln Arg Ala Cys Glu Ser Gly Pro Cys Pro
         1370                1375                1380
35
   cag tgg gct tat ggc aac tgg gga gag tgc act aag ctg tgt ggt gga   4229
   Gln Trp Ala Tyr Gly Asn Trp Gly Glu Cys Thr Lys Leu Cys Gly Gly
      1385                1390                1395

40 ggc ata aga aca aga ctg gtg gtc tgt cag cgg tcc aac ggt gaa cgg   4277
   Gly Ile Arg Thr Arg Leu Val Val Cys Gln Arg Ser Asn Gly Glu Arg
   1400               1405                1410                1415

   ttt cca gat ttg agc tgt gaa att ctt gat aaa cct ccc gat ggt gag   4325
45 Phe Pro Asp Leu Ser Cys Glu Ile Leu Asp Lys Pro Pro Asp Arg Glu
                  1420                1425                1430

   cag tgt aac aca cat gct tgt cca cac gac gct gca tgg agt act ggc   4373
   Gln Cys Asn Thr His Ala Cys Pro His Asp Ala Ala Trp Ser Thr Gly
50            1435                1440                1445

   cct tgg agc tcg tgt tct gtc tct tgt ggt cga ggg cat aaa caa cga   4421
   Pro Trp Ser Ser Cys Ser Val Ser Cys Gly Arg Gly His Lys Gln Arg
         1450                1455                1460
55
   aat gtt tac tgc atg gca aaa gat gga agc cat tta gaa agt gat tac   4469
   Asn Val Tyr Cys Met Ala Lys Asp Gly Ser His Leu Glu Ser Asp Tyr

   [illegible]
   Arg Tyr Tyr Lys Trp Lys Ala Gly Ala Trp Ser Gln Cys Ser Val Thr
                  1500                1505                1510
```

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   tgt ggc cga ggc gta cag cag agg cat gtg ggc tgt cag atc gga aca   4613
   Cys Gly Arg Gly Val Gln Gln Arg His Val Gly Cys Gln Ile Gly Thr
              1515                1520                1525
 5
   cac aaa ata gcc aga gac acc gag tgc aac cca tac acc aga ccg gag   4661
   His Lys Ile Ala Arg Asp Thr Glu Cys Asn Pro Tyr Thr Arg Pro Glu
          1530                1535                1540

10 tcg gaa tgc gaa tgc caa ggc cca cgg tgt ccc ctt tac act tgg agg   4709
   Ser Glu Cys Glu Cys Gln Gly Pro Arg Cys Pro Leu Tyr Thr Trp Arg
      1545                1550                1555

   gca gag gaa tcg caa gaa tgc acc aag acc tgc ggc gaa ggc tcc agg   4757
15 Ala Glu Glu Ser Gln Glu Cys Thr Lys Thr Cys Gly Glu Gly Ser Arg
   1560                1565                1570                1575

   tac cgc aaq gtq qtq tgt gtg gat gac aac aaa aac gaq gtq cat ggq   4805
   Tyr Arg Lys Val Val Cys Val Asp Asp Asn Lys Asn Glu Val His Gly
20                 1580                1585                1590

   gca cgc tgt gac gtg agc aag cgg ccg gtg gac cgt gaa agc tgt agt   4853
   Ala Arg Cys Asp Val Ser Lys Arg Pro Val Asp Arg Glu Ser Cys Ser
              1595                1600                1605
25
   ttg caa ccc tgc gag tat gtc tgg atc aca gga gaa tgg tca gag tgc   4901
   Leu Gln Pro Cys Glu Tyr Val Trp Ile Thr Gly Glu Trp Ser Glu Cys
          1610                1615                1620

30 tca gtg acc tgt gga aaa ggc tac aaa caa agg ctt gtc tcg tgc agc   4949
   Ser Val Thr Cys Gly Lys Gly Tyr Lys Gln Arg Leu Val Ser Cys Ser
      1625                1630                1635

   gag att tac acc ggg aaa gag aat tat gaa tac agc tac caa acc acc   4997
35 Glu Ile Tyr Thr Gly Lys Glu Asn Tyr Glu Tyr Ser Tyr Gln Thr Thr
   1640                1645                1650                1655

   atc aac tgc cca ggc acg cag ccc ccc agt gtt cac ccc tgt tac ctg   5045
   Ile Asn Cys Pro Gly Thr Gln Pro Pro Ser Val His Pro Cys Tyr Leu
40                 1660                1665                1670

   agg gag tgc cct gtc tcg gcc acc tgg aga gtt ggc aac tgg ggg agc   5093
   Arg Glu Cys Pro Val Ser Ala Thr Trp Arg Val Gly Asn Trp Gly Ser
              1675                1680                1685
45
   tgc tca gtg tct tgt ggt gtt gga gtg atg cag aga tct gtg caa tgt   5141
   Cys Ser Val Ser Cys Gly Val Gly Val Met Gln Arg Ser Val Gln Cys
          1690                1695                1700

50 tta aac aat gag gac caa ccc agc cac tta tgc cac act gat ctg aag   5189
   Leu Thr Asn Glu Asp Gln Pro Ser His Leu Cys His Thr Asp Leu Lys
      1705                1710                1715

   cca gaa gaa cga aaa acc tgc cgt aat gtc tat aac tgt gag tta ccc   5237
55 Pro Glu Glu Arg Lys Thr Cys Arg Asn Val Tyr Asn Cys Glu Leu Pro
   1720                1725                1730                1735
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   Gly Met His Ser Asp His Pro Lys Glu Tyr Val Thr Leu Val His Gly
          1770                1775                1780

   gac tct gag aat ttc tcc gag gtt tat ggg cac agg tta cac aac cca   5429
 5 Asp Ser Glu Asn Phe Ser Glu Val Tyr Gly His Arg Leu His Asn Pro
      1785                1790                1795

   aca gaa tgt ccc tat aac ggg agc cgg cgc gat gac tgc caa tgt cgg   5477
   Thr Glu Cys Pro Tyr Asn Gly Ser Arg Arg Asp Asp Cys Gln Cys Arg
10 1800                1805                1810                1815

   aag gat tac acg gcc gct ggg ttt tcc agt ttt cag aaa atc aga ata   5525
   Lys Asp Tyr Thr Ala Ala Gly Phe Ser Ser Phe Gln Lys Ile Arg Ile
                  1820                1825                1830
15
   gac ctg acc agc atg cag ata atc acc act gac tta cag ttt gca agg   5573
   Asp Leu Thr Ser Met Gln Ile Ile Thr Thr Asp Leu Gln Phe Ala Arg
             1835                1840                1845

20 aca agc gaa gga cat ccc gtc cct ttt gcc aca gcc ggg gat tgc tac   5621
   Thr Ser Glu Gly His Pro Val Pro Phe Ala Thr Ala Gly Asp Cys Tyr
          1850                1855                1860

   agc gct gcc aag tgc cca cag ggt cgt ttt agc atc aac ctt tat gga   5669
25 Ser Ala Ala Lys Cys Pro Gln Gly Arg Phe Ser Ile Asn Leu Tyr Gly
      1865                1870                1875

   acc ggc ttg tct tta act gaa tct gcc aga tgg ata tca caa ggg aat   5717
   Thr Gly Leu Ser Leu Thr Glu Ser Ala Arg Trp Ile Ser Gln Gly Asn
30 1880                1885                1890                1895

   tat gct gtc tct gac att aag aag tcg ccg gat ggt acc cga gtc gta   5765
   Tyr Ala Val Ser Asp Ile Lys Lys Ser Pro Asp Gly Thr Arg Val Val
                  1900                1905                1910
35
   ggg aaa tgc ggt ggt tac tgt gga aaa tgc act cca tcc tct ggt act   5813
   Gly Lys Cys Gly Gly Tyr Cys Gly Lys Cys Thr Pro Ser Ser Gly Thr
             1915                1920                1925

40 ggc ctg gag gtg cga gtt tta tagctaaggt gctttgaaga ggaagccatt      5864
   Gly Leu Glu Val Arg Val Leu
          1930

   atggatggat gaaggataqt aatgcaatac ctccacctta atttgggtgc atgtgtatgt 5924
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   gtgtgtgtgt ttgtgtgtga ctttgtatgat tgtgtgtgta aatgtgtgta catatacata 5984

   tatata                                                            5990

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   <211> 1934
   <212> PRT
   <213> Homo sapiens ADAMTS-9b
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   <400> 26
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    1               5                  10                  15

   Glu Ile Val Leu Phe Ile Arg Val Asn Ala Leu Gly Arg Pro Phe
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        50                  55                  60

    Thr Asn Val His Phe Lys Arg Thr Arg Arg Ser Ile Asn Ser Ala Thr
     65                  70                  75                  80
 5
    Asp Pro Trp Pro Ala Phe Ala Ser Ser Ser Ser Ser Ser Thr Ser Pro
                    85                  90                  95

    Gln Ala His Tyr Arg Leu Ser Ala Phe Gly Gln Gln Phe Leu Phe Asn
10              100                 105                 110

    Leu Thr Ala Asn Ala Gly Phe Ile Ala Pro Leu Phe Thr Val Thr Leu
            115                 120                 125

15  Leu Gly Thr Pro Gly Val Asn Gln Thr Lys Phe Tyr Ser Glu Glu Glu
        130                 135                 140

    Ala Glu Leu Lys His Cys Phe Tyr Lys Gly Tyr Val Asn Thr Asn Ser
    145                 150                 155                 160
20
    Glu His Thr Ala Val Ile Ser Leu Cys Ser Gly Met Leu Gly Thr Phe
                    165                 170                 175

    Arg Ser His Asp Gly Gly Tyr Phe Ile Glu Pro Leu Gln Ser Met Asp
25              180                 185                 190

    Glu Gln Glu Asp Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg
            195                 200                 205

30  Arg Ser Ala Pro Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp
        210                 215                 220

    Thr Ser Glu His Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg
    225                 230                 235                 240
35
    Ala Arg Lys Trp Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala
                    245                 250                 255

    Leu Asn Ser Gly Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys
40              260                 265                 270

    Thr Asp Asn Thr Arg Glu Lys Arg Thr His Arg Arg Thr Lys Arg Phe
            275                 280                 285

45  Leu Ser Tyr Pro Arg Phe Val Glu Val Leu Val Val Ala Asp Asn Arg
        290                 295                 300

    Met Val Ser Tyr His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu
    305                 310                 315                 320
50
    Met Ser Ile Val Ala Ser Ile Tyr Lys Asp Pro Ser Ile Gly Asn Leu
                    325                 330                 335

    Ile Asn Ile Val Ile Val Asn Leu Ile Val Ile His Asn Glu Gln Asp
55              340                 345                 350

    Gly Pro Ser Ile Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Phe Cys
            355                 360                 365

    Thr Leu Gly Leu Ala Glu Leu Gly Thr Leu Lys Asp Trp Tyr Arg Phe
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405 410 415

Cys Ser Ile Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile Ala
420 425 430

His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Asn Asn Lys
435 440 445

Cys Lys Glu Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro Thr
450 455 460

Leu Asn Phe Tyr Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg Lys
465 470 475 480

Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn
485 490 495

Glu Pro Glu Ser Arg Pro Tyr Pro Leu Pro Val Gln Leu Pro Gly Ile
500 505 510

Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly Ser
515 520 525

Gln Val Cys Pro Tyr Met Met Gln Cys Arg Arg Leu Trp Ser Asn Asn
530 535 540

Val Asn Gly Val His Lys Gly Cys Arg Thr Gln His Thr Pro Trp Ala
545 550 555 560

Asp Gly Thr Glu Cys Glu Pro Gly Lys His Cys Lys Tyr Gly Phe Cys
565 570 575

Val Pro Lys Glu Met Asp Val Pro Val Thr Asp Gly Ser Trp Gly Ser
580 585 590

Trp Ser Pro Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile Lys
595 600 605

Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly Lys
610 615 620

Tyr Cys Val Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu Pro
625 630 635 640

Cys Leu Lys Gln Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His Phe
645 650 655

Asp Gly Lys His Phe Asn Ile Asn Gly Leu Leu Pro Asn Val Arg Trp
660 665 670

Val Pro Lys Tyr Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu Phe
675 680 685

Cys Arg Val Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg Val
690 695 700

Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val Gln
705 710 715 720

Ile Leu Ala Gly Thr Pro Asn Thr Val His Lys Gly Tyr Asn Thr Val

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          755                 760                 765

   Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His Ser
       770                 775                 780
 5
   Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser Ser
   785                 790                 795                 800

   Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala Lys
10                 805                 810                 815

   Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser Glu
               820                 825                 830

15 Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu Leu
           835                 840                 845

   Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val Arg
       850                 855                 860
20
   Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr Trp
   865                 870                 875                 880

   Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly Glu
25                 885                 890                 895

   Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr Val
               900                 905                 910

30 Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr Glu
           915                 920                 925

   Pro Cys Gly Thr Gly Cys Asp Leu Arg Trp His Val Ala Ser Arg Ser
       930                 935                 940
35
   Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile Tyr
   945                 950                 955                 960

   Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp Asp
40                 965                 970                 975

   Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys Ser
               980                 985                 990

45 Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu Cys
           995                1000                1005

   Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile Cys Val
      1010                1015                1020
50
   Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His Gln Glu
   1025                1030                1035                1040

   Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln Trp Lys
55                 1045                1050                1055

   Ser Gly Asp Trp Ser Glu Cys Leu Val Thr Cys Gly Lys Gly His Lys

60

   His Glu Met Ala Ser Trp Gln Ala Gly Ile Trp Val Gln Cys Ser Val
```

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1105                1110                1115                1120

Thr Cys Gly Gln Gly Tyr Gln Leu Arg Ala Val Lys Cys Ile Ile Gly
                1125                1130                1135

Thr Tyr Met Ser Val Val Asp Asp Asn Asp Cys Asn Ala Ala Thr Arg
            1140                1145                1150

Pro Thr Asp Thr Gln Asp Cys Glu Leu Pro Ser Cys His Pro Pro Pro
        1155                1160                1165

Ala Ala Pro Glu Thr Arg Arg Ser Thr Tyr Ser Ala Pro Arg Thr Gln
    1170                1175                1180

Trp Arg Phe Gly Ser Trp Thr Pro Cys Ser Ala Thr Cys Gly Lys Gly
1185                1190                1195                1200

Thr Arg Met Arg Tyr Val Ser Cys Arg Asp Glu Asn Gly Ser Val Ala
                1205                1210                1215

Asp Glu Ser Ala Cys Ala Thr Leu Pro Arg Pro Val Ala Lys Glu Glu
            1220                1225                1230

Cys Ser Val Thr Pro Cys Gly Gln Trp Lys Ala Leu Asp Trp Ser Ser
        1235                1240                1245

Cys Ser Val Thr Cys Gly Gln Gly Arg Ala Thr Arg Gln Val Met Cys
    1250                1255                1260

Val Asn Tyr Ser Asp His Val Ile Asp Arg Ser Glu Cys Asp Gln Asp
1265                1270                1275                1280

Tyr Ile Pro Glu Thr Asp Gln Asp Cys Ser Met Ser Pro Cys Pro Gln
                1285                1290                1295

Arg Thr Pro Asp Ser Gly Leu Ala Gln His Pro Phe Gln Asn Glu Asp
            1300                1305                1310

Tyr Arg Pro Arg Ser Ala Ser Pro Ser Arg Thr His Val Leu Gly Gly
        1315                1320                1325

Asn Gln Trp Arg Thr Gly Pro Trp Gly Ala Cys Ser Ser Thr Cys Ala
    1330                1335                1340

Gly Gly Ser Gln Arg Arg Val Val Val Cys Gln Asp Glu Asn Gly Tyr
1345                1350                1355                1360

Thr Ala Asn Asp Cys Val Glu Arg Ile Lys Pro Asp Ser Gln Arg Ala
                1365                1370                1375

Cys Glu Ser Gly Pro Cys Pro Gln Trp Ala Tyr Gly Asn Trp Gly Glu
            1380                1385                1390

Cys Thr Lys Leu Cys Gly Gly Gly Ile Arg Thr Arg Leu Val Val Cys
        1395                1400                1405

Gln Arg Ser Asn Gly Glu Arg Phe Pro Asp Leu Ser Cys Glu Ile Leu
    1410                1415                1420

                1425                1430                1435

Gly Arg Gly His Lys Gln Arg Asn Val Tyr Cys Met Ala Lys Asp Gly
```

```
                1460                1465                1470

    Ser His Leu Glu Ser Asp Tyr Cys Lys His Leu Ala Lys Pro His Gly
            1475                1480                1485
 5
    His Arg Lys Cys Arg Gly Gly Arg Cys Pro Lys Trp Lys Ala Gly Ala
        1490                1495                1500

    Trp Ser Gln Cys Ser Val Ser Cys Gly Arg Gly Val Gln Gln Arg His
10  1505                1510                1515                1520

    Val Gly Cys Gln Ile Gly Thr His Lys Ile Ala Arg Asp Thr Glu Cys
                    1525                1530                1535

15  Asn Pro Tyr Thr Arg Pro Glu Ser Glu Cys Glu Cys Gln Gly Pro Arg
                1540                1545                1550

    Cys Pro Leu Tyr Thr Trp Arg Ala Glu Glu Ser Gln Glu Cys Thr Lys
            1555                1560                1565
20
    Thr Cys Gly Glu Gly Ser Arg Tyr Arg Lys Val Val Cys Val Asp Asp
        1570                1575                1580

    Asn Lys Asn Glu Val His Gly Ala Arg Cys Asp Val Ser Lys Arg Pro
25  1585                1590                1595                1600

    Val Asp Arg Glu Ser Cys Ser Leu Gln Pro Cys Glu Tyr Val Trp Ile
                    1605                1610                1615

30  Thr Gly Glu Trp Ser Glu Cys Ser Val Thr Cys Gly Lys Gly Tyr Lys
                1620                1625                1630

    Gln Arg Leu Val Ser Cys Ser Glu Ile Tyr Thr Gly Lys Glu Asn Tyr
            1635                1640                1645
35
    Glu Tyr Ser Tyr Gln Thr Thr Ile Asn Cys Pro Gly Thr Gln Pro Pro
        1650                1655                1660

    Ser Val His Pro Cys Tyr Leu Arg Glu Cys Pro Val Ser Ala Thr Trp
40  1665                1670                1675                1680

    Arg Val Gly Asn Trp Gly Ser Cys Ser Val Ser Cys Gly Val Gly Val
                    1685                1690                1695

45  Met Gln Arg Ser Val Gln Cys Leu Thr Asn Glu Asp Gln Pro Ser His
                1700                1705                1710

    Leu Cys His Thr Asp Leu Lys Pro Leu Glu Arg Lys Thr Cys Arg Asn
            1715                1720                1725
50
    Val Tyr Asn Cys Glu Leu Pro Gln Asn Cys Lys Glu Val Lys Arg Leu
        1730                1735                1740

    Lys Gly Ala Ser Glu Asp Gly Glu Tyr Phe Leu Met Ile Arg Gly Lys
55  1745                1750                1755                1760

    Leu Leu Lys Ile Phe Cys Ala Gly Met His Ser Asp His Pro Lys Glu
                    1765                1770                1775

    Arg Asp Asp Cys Asn Glu Arg Lys Asp Thr Thr Ala Ala Gly Phe Met
```

1810 1815 1820

Ser Phe Gln Lys Ile Arg Ile Asp Leu Thr Ser Met Gln Ile Ile Thr
1825 1830 1835 1840

Thr Asp Leu Gln Phe Ala Arg Thr Ser Glu Gly His Pro Val Pro Phe
1845 1850 1855

Ala Thr Ala Gly Asp Cys Tyr Ser Ala Ala Lys Cys Pro Gln Gly Arg
1860 1865 1870

Phe Ser Ile Asn Leu Tyr Gly Thr Gly Leu Ser Leu Thr Glu Ser Ala
1875 1880 1885

Arg Trp Ile Ser Gln Gly Asn Tyr Ala Val Ser Asp Ile Lys Lys Ser
1890 1895 1900

Pro Asp Gly Thr Arg Val Val Gly Lys Cys Gly Gly Tyr Cys Gly Lys
1905 1910 1915 1920

Cys Thr Pro Ser Ser Gly Thr Gly Leu Glu Val Arg Val Leu
1925 1930